nature portfolio

https://doi.org/10.1038/s41586-024-08004-9

Supplementary information

Stereospecific radical coupling with a non-natural photodecarboxylase

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Stereospecific Radical Coupling Enabled by a Non-Natural Photodecarboxylase

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Supplementary Information

Table of Contents

Materials and Methods

General information. The NMR spectra were recorded at 300 MHz, 400 MHz, and 500 MHz for ^{1}H, at 75 MHz, 101 MHz and 125 MHz for ^{13}C, at 376 MHz for ^{19}F. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvents ($CHCl_3$ @ 7.26 ppm ^{1}H NMR, 77.16 ppm ^{13}C NMR). Coupling constants (*J*) are given in Hz, and are quoted to the nearest 0.5 Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; sext, sextet; m, multiplet. Additionally, signals can be described as broad (br) and apparent (app).

High-resolution mass spectra (HRMS) were obtained from the ICIQ High Resolution Mass Spectrometry Unit on MicroTOF Focus and Maxis Impact (Bruker Daltonics) with electrospray ionization. Proteins in their native state were characterized by size-exclusion chromatography (SEC) combined with native mass spectrometry (nMS), using an Acquity APC XT 45 A. This analysis was outsourced to Dr. Andrea Gargano's team at the University of Amsterdam. Optical rotations were measured on a Polarimeter Jasco P-1030 and are reported as follows: $[\alpha]_D^T$ (c in g per 100 mL, solvent).

Cell growing and enzyme expression were performed in a standard INFORS-HT multitron incubator with an orbital of 50 mm. Cells lysis was performed with a Thermo Fisher ultrasonicator 120 W. Centrifugation was performed with a Thermo Fisher SORVALL ST16R centrifuge equipped with different rotors. When applicable, enzyme concentration was determined using a Nanodrop™ One from Thermo Fisher Scientific. PCR reactions were performed using MiniAmp thermal cycler from applied biosystems. The optical density (OD) was measured in a Cell Density Meter Model 40 from Thermo Fisher. LB broth was sterilized with a 75 L Autoclave Sterilmatic (AE-75-DRY) from Thermo Fisher. Mini-PROTEAN™ SDS-Acrylamide Electrophoresis equipment was purchased from BIO-RAD.

The authors are indebted to the team of the Research Support Area at ICIQ.

Determination of Yield and Diastereomeric Ratio: GC-FID analyses were performed on an Agilent 7890A GC using HP5 column or Shimadzu GC-2010+AOC-20i using OPTIMA 5MS column. GC-FID traces of the performed enzymatic analytical scale reactions were compared to the synthesized reference samples of products **3** and **5** (see *Section H* for the preparation of reference compounds). Yields and diastereomeric ratio were determined using the corresponding response factor (see section I.2 and I.3). The reactions were analyzed using the following conditions: HP5-column 30m x 0.25mm x 0.25µm, constant pressure: 16.4 psi, split ratio: 40:1, T injector: 250 °C. Temperature Program: T initial 50 °C, hold 5 min, gradient 20 °C/min up to 325 °C; hold 5 min. OPTIMA 5MS column 30m x 0.25mm x 0.25µm, constant pressure: 158.7 kPa, split ratio: 40:1, T injector: 250 °C. Temperature Program: T initial 120 °C, hold 2 min, gradient 20 °C/min up to 280 °C; hold 2 min.

Determination of Enantiomeric Purity: UPC^2 analyses on chiral stationary phase were performed on a Waters ACQUITY® UPC^2 instrument, using Daicel Chiralpak IC-3, IB-3, IE-3 or IA-3 chiral columns. The exact conditions for the analysis of compounds **3** and **5** are specified within the characterization section. UPC^2 traces were compared to racemic samples for each diastereomer of compounds **5**, which were prepared by running the reactions under the conditions specified in *Section H* of the Supplementary Information.

Materials

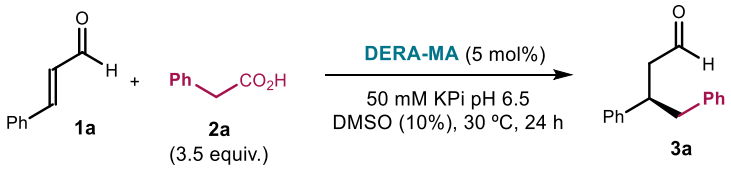
HisTrap™ HP chromatography columns for enzyme purification were purchased from Cytiva. HiTrap™ DEAE FF columns for ion exchange chromatography were purchased from GE Healthcare. PD-10 columns containing Sephadex™ G-25 M for buffer exchange were purchased

from Cytiva. LB Broth powder was purchased from Nzytech. Customized genes encoding for the enzymes used in this study were purchased from GenScript BL21(DE3). Competent cells, Monarch plasmid miniprep kit, and Q5 site directed mutagenesis kit were purchased from New England BioLabs$_{Inc}$. QuikChange II-E site-directed mutagenesis Kit was purchased from Agilent. Customized primers were purchuased from Biomers. Coomassie R250 powder was purchased from BIO-RAD. Protein ladders and standard markers were purchased from BIO-RAD. Commercial grade reagents and solvents were purchased at the highest commercial quality from Sigma Aldrich or Alfa Aesar and used as received, unless otherwise stated. Cinnamaldehyde **1a** was purchased from Sigma Aldrich, distilled prior to use and stored in a closed vial under argon at -20 ºC. Substrates **1d, 1e**, **2a-i** and chiral acid **4a** were purchased from TCI, Alfa Aesar and Sigma Aldrich, respectively, and used as received. The synthetic procedures for the preparation of substrates **1** and **4** are reported in *Section G* of the Supplementary Information. The synthetic procedures for the preparation of reference products **3** and **5** are reported in *Section H* of the Supplementary Information.

A. Optimization Studies

A.1 Biocatalytic Enantioselective Reaction leading to Product 3a

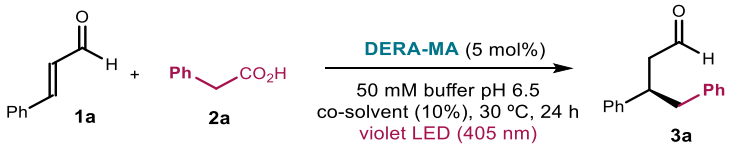
Table S1. Optimization of the light source



entry	**1a**:**2a**	wavelength	yield **3a** %
1	1:3.5	**365**	10
2	1:3.5	**380**	25
3	1:3.5	**405**	33
4	1:3.5	**420**	<1
5	1:3.5	**460**	<1

Reactions performed with 5 mol% of DERA-MA (125 µM) on a 1.25 µmol scale of 1a (2.5 mM) in 50 mM phosphate buffer at pH 6.5 in 10% of DMSO for 24h at 30 ºC.

Table S2. Further optimization studies



entry	**1a**:**2a**	cosolvent	buffer 50 mM	yield **3a** %
1	**2:1**	10% DMSO	KPi pH 6.5	7
2	**1:1**	10% DMSO	KPi pH 6.5	9
3	**1:2**	10% DMSO	KPi pH 6.5	17
4	**1:3.5**	10% DMSO	KPi pH 6.5	33
5	**1:5**	10% DMSO	KPi pH 6.5	24
6	**1:10**	10% DMSO	KPi pH 6.5	17
7	1:3.5	**10% DMF**	KPi pH 6.5	14
8	1:3.5	**10% DMA**	KPi pH 6.5	11
9	1:3.5	**10% EG**	KPi pH 6.5	15
10	1:3.5	10% DMSO	**Tris pH 7.4**	13
11	1:3.5	20% DMSO	**MOPS pH 6.5**	26
12	1:3.5	20% DMSO	**MES pH 6.5**	22
13	1:3.5	20% DMSO	**ACES pH 6.5**	26

Reactions performed with 5 mol% of DERA-MA (125 µM) on a 1.25 µmol scale of 1a (2.5 mM) for 24h at 30 ºC using violet LED at 405 nm.

A.2 Control Experiments

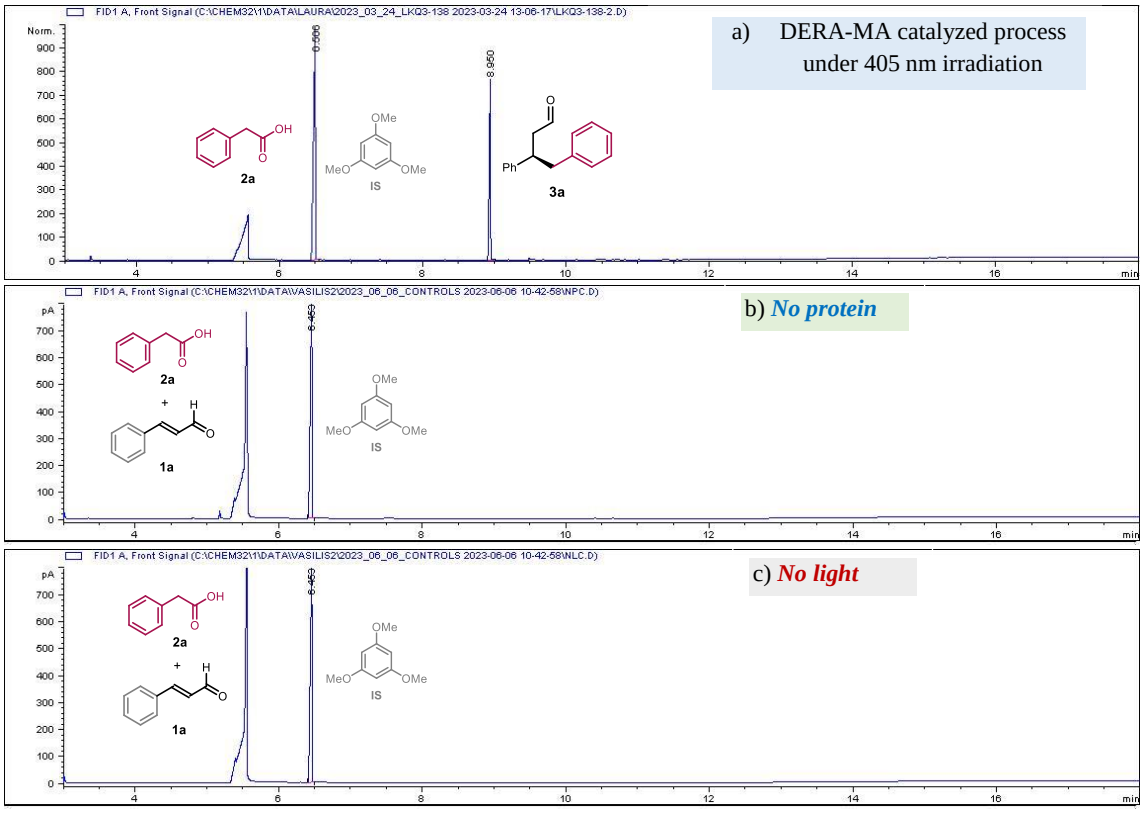
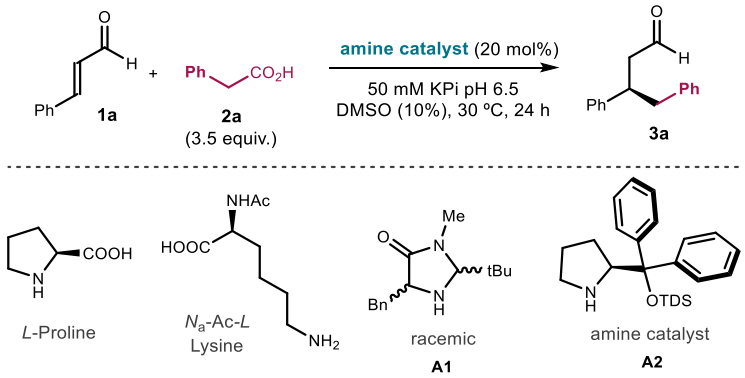


Figure S1: GC-FID data for the photoenzymatic reaction of **1a** and **2a** catalyzed by DERA-MA^{S18A}. Reactions performed: a) under optimal conditions (irradiation at 405 nm), b) without enzyme, and c) without light irradiation. Retention time of product **3a**: 8.95 min; 1,3,5-trimethoxybenzene used as the internal standard.

Table S3. Control experiments with different small amine organocatalysts.



In all cases: ***No reaction***

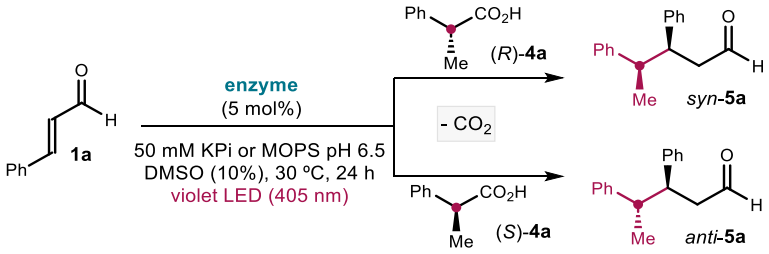
Entry	Aminocatalyst	Yield **3a** %
1	*L*-Proline	0
2	*N*-Ac-Lysine	0
3	**A-1**	0
4	**A-2**	0

Reactions performed with 20 mol% of aminocatalyst on a 1.25 µmol scale of **1a** (2.5 mM) for 24 hours at 30ºC using violet LED at 405 nm.

A.3 Biocatalytic Enantioselective Reaction leading to Product 5a

Screening of rationally designed DERA-MA variants with the chiral acid 4a

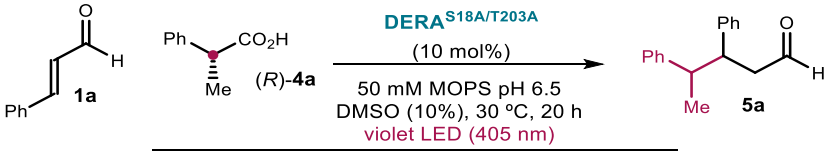
Table S4: Screening of DERA-MA variants as purified enzymes



Entry	Enzyme	Substrate	yield **5a** (%)	*anti*:*syn*
1	DERA-MA	(*S*)-**4a**	17	2.8:1
2	DERA-MA	(*R*)-**4a**	39	1:1.6
1	DERA-MA^{S18A}	(*S*)-**4a**	11	4.5:1
2	DERA-MA^{S18A}	(*R*)-**4a**	36	1:4
3	DERA-MA^{S18G}	(*S*)-**4a**	41	1.3:1
4	DERA-MA^{S18G}	(*R*)-**4a**	46	1:1.6
5	DERA-MA^{S18V}	(*S*)-**4a**	11	2.8:1
6	DERA-MA^{S18V}	(*R*)-**4a**	28	1:1.2
7	DERA-MA^{S238A}	(*S*)-**4a**	6	2.1:1
8	DERA-MA^{S238A}	(*R*)-**4a**	25	1.4:1
9	DERA-MA^{T203A}	(*S*)-**4a**	21	5.3:1
10	DERA-MA^{T203A}	(*R*)-**4a**	32	1:4.3
11	DERA-MA^{L172A}	(*S*)-**4a**	7	2.4:1
12	DERA-MA^{L172A}	(*R*)-**4a**	21	1.3:1
13	DERA-MA^{Y49A}	(*S*)-**4a**	11	2:1
14	DERA-MA^{Y49A}	(*R*)-**4a**	33	1.3:1
15	DERA-MA$^{S18A/T203A}$	(*S*)-**4a**	38	15:1
16	DERA-MA$^{S18A/T203A}$	(*R*)-**4a**	62	1:7.5
17	DERA-MA$^{S18A/T203V}$	(*S*)-**4a**	9	4.3:1
18	DERA-MA$^{S18A/T203V}$	(*R*)-**4a**	70	1:8.3
19	DERA-MA$^{S18A/T203A/S238A}$	(*S*)-**4a**	27	18.2:1
20	DERA-MA$^{S18A/T203A/S238A}$	(*R*)-**4a**	36	1:4.5

Reactions performed with 5 mol% of enzymes (125 µM) on a 1.25 µmol scale of 1a (2.5 mM) in 50 mM phosphate buffer or 50 mM MOPS buffer at pH 6.5 in 10% of DMSO for 24 h. Ee of **5a** is 99%.

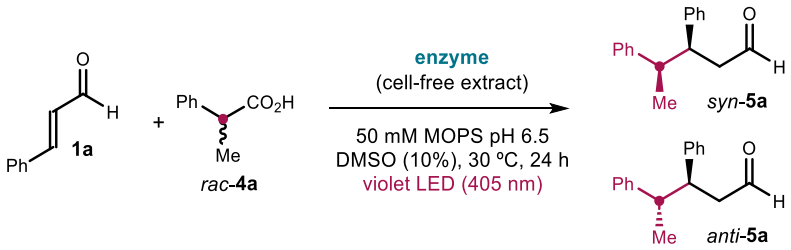
Table S5. Effect of cinnamaldehyde's stoichiometry



entry	Ratio **1a:4a**	yield **5a** %
1	1:3.5	82
2	1:1	12
3	2:1	7

Reactions performed with 10 mol% of enzymes (125 µM) on a 0.63 µmol scale of 1a (1.25 mM) in 50 mM MOPS buffer at pH 6.5 in 10% of DMSO for 20 h. ee of **5a** is 99%.

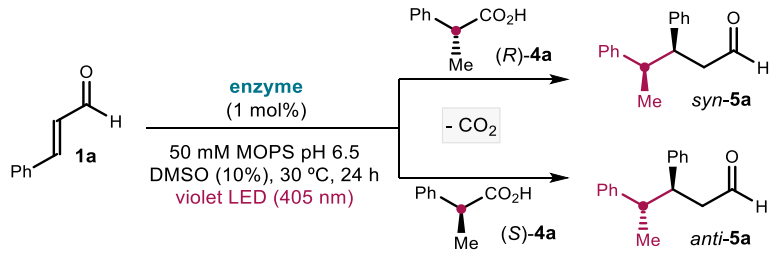
Table S6: Screening of DERA-MA variants as cell-free extracts for developing a kinetic resolution



Entry	**Enzyme**	**1a:4a**	Yield **5a** (%)	*anti:syn*
1	S18A_T203V	1:3.5	12	1:5.3
2	S18A_T203L	1:3.5	14	1:2
3	S18A_T203I	1:3.5	<1	n.d.

Reactions performed with of enzymes as cell-free extracts on a 1.25 µmol scale of 1a (2.5 mM) in 50 mM MOPS buffer at pH 6.5 in 10% of DMSO for 24 h

Table S7: Activity testing of purified DERA-MA variants at 1 mol% concentration



Entry	Enzyme	Substrate	Conversion to **5a** (%)	*anti:syn*	TON	ee
1	DERA-MA$^{S18A/T203A}$	(*S*)-**4a**	6	9.5:1	6	>99%
2	DERA-MA$^{S18A/T203A}$	(*R*)-**4a**	10	1:7.1	10	>99%
3	DERA-MA$^{S18A/T203A/G239N}$	(*S*)-**4a**	10	13.4:1	10	>99%
4	DERA-MA$^{S18A/T203A/G239N}$	(*R*)-**4a**	18	1:8.6	18	>99%
5	DERA-MA$^{S18A/T203A/G239E}$	(*S*)-**4a**	10	12.8:1	10	>99%
6	DERA-MA$^{S18A/T203A/G239E}$	(*R*)-**4a**	19	1:8	19	>99%
7	DERA-MA$^{S18A/T203A/G239A}$	(*S*)-**4a**	18	21.5:1	18	>99%
8	DERA-MA$^{S18A/T203A/G239A}$	(*R*)-**4a**	17	1:9.8	17	>99%
9	DERA-MA$^{S18A/T203A/G239L}$	(*S*)-**4a**	13	19.1:1	13	>99%
10	DERA-MA$^{S18A/T203A/G239L}$	(*R*)-**4a**	16	1:10.2	16	N.D.
11	DERA-MA$^{S18A/Y49V/T203A}$	(*S*)-**4a**	6	9.1:1	6	N.D.
12	DERA-MA$^{S18A/Y49V/T203A}$	(*R*)-**4a**	11	1:8.9	11	N.D.
13	DERA-MA$^{S18A/Y49L/T203A}$	(*S*)-**4a**	6	7.2:1	6	N.D.
14	DERA-MA$^{S18A/Y49L/T203A}$	(*R*)-**4a**	13	1:8.3	13	N.D.
15	DERA-MA$^{S18A/Y49F/T203A}$	(*S*)-**4a**	7	6.4:1	7	>99%
16	DERA-MA$^{S18A/Y49F/T203A}$	(*R*)-**4a**	14	1:7.8	14	>99%
17	DERA-MA^{S52Y}	(*S*)-**4a**	5	1.9:1	5	N.D.
18	DERA-MA^{S52Y}	(*R*)-**4a**	21	1:1.3	21	66% (syn), >99% (anti)
19	DERA-MA$^{S18A/S52G/T203A}$	(*S*)-**4a**	7	13.2:1	7	N.D.
20	DERA-MA$^{S18A/S52G/T203A}$	(*R*)-**4a**	18	1:10	18	>99%
21	DERA-MA$^{S18A/S52F/T203A}$	(*S*)-**4a**	9	11.9:1	9	>99%
22	DERA-MA$^{S18A/S52F/T203A}$	(*R*)-**4a**	11	1:7.2	11	N.D.
23	DERA-MA$^{S18A/S52H/T203A}$	(*S*)-**4a**	10	11.1:1	10	>99%
24	DERA-MA$^{S18A/S52H/T203A}$	(*R*)-**4a**	11	1:6.8	11	N.D.
25	DERA-MA$^{S142T/A206V}$	(*S*)-**4a**	6	1.8:1	6	N.D.
26	DERA-MA$^{S142T/A206V}$	(*R*)-**4a**	18	1:1.7	18	>99%
27	DERA-MA$^{S142T/V173A/A206V}$	(*S*)-**4a**	7	1.9:1	7	N.D.
28	DERA-MA$^{S142T/V173A/A206V}$	(*R*)-**4a**	22	1:1.8	22	>99%

Reactions performed with 1 mol% of enzymes (12.5 µM) on a 0.63 µmol scale of 1a (1.25 mM) in 50 mM MOPS buffer at pH 6.5 in 10% of DMSO for 24 h. N.D.: not determined

B. Unsuccessful and Low Yielding Substrates

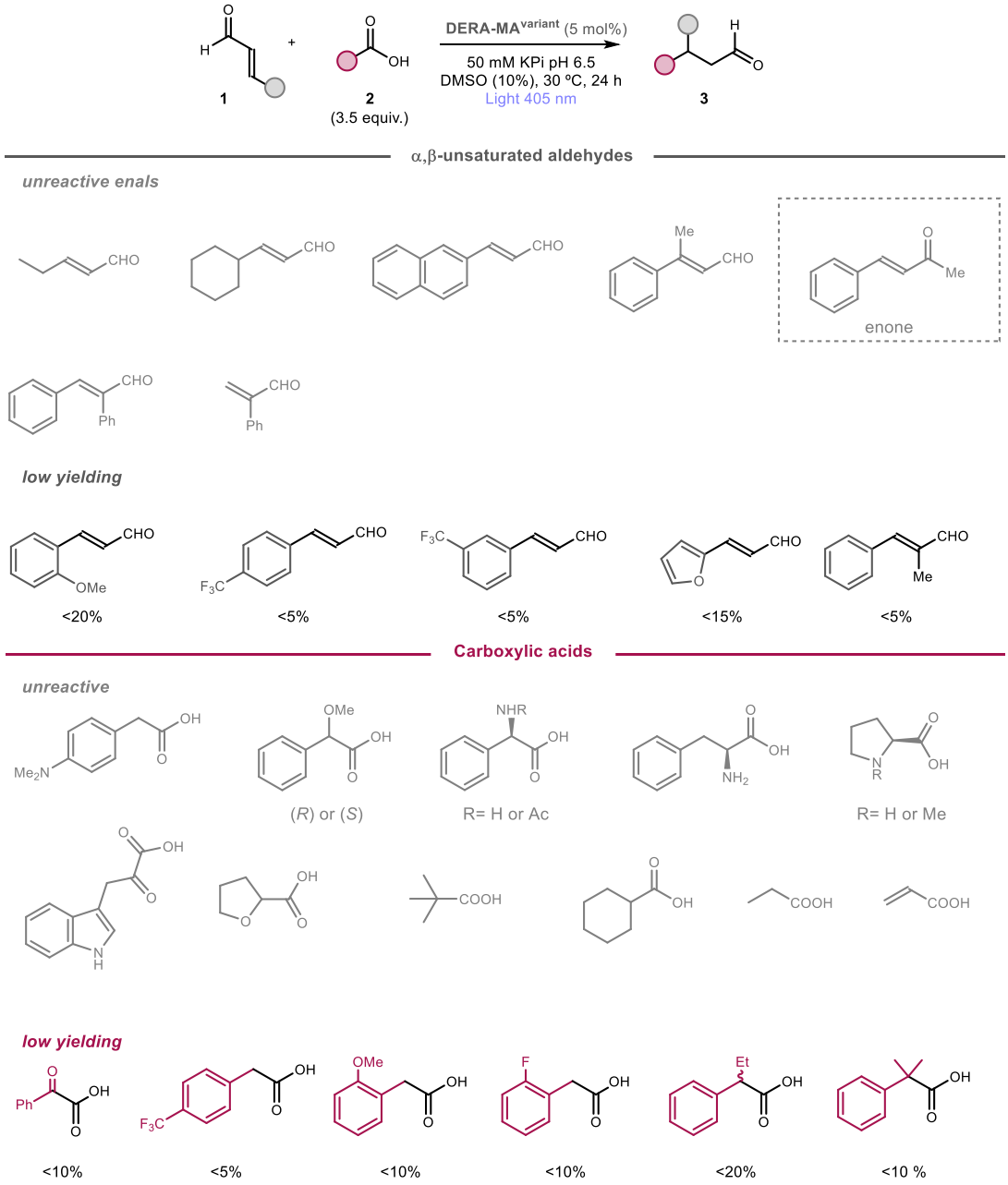


Figure S2: Failed and low-yielding substrates for the radical coupling using DERA-MA variant. Yields were estimated using the average response factor obtained with 1,3,5-trimethoxybenzene as internal standard.

C. Mutagenesis Procedures

C.1 Rationally designed variants

The DERA-MA variants were obtained by site-directed mutagenesis using either the QuickChange II site-directed mutagenesis kit (Agilent Technologies), according to the procedure A below, or the Q5 site-directed mutagenesis kit (NEB), according to procedure B below. For both procedures the following DNA template (pET26b containing DERA-MA sequence shown in bold) was used after extraction from BL21(DE3) *E.coli* cells using the Monarch plasmid miniprep kit (NEB) according to manufacturer´s instructions.

The primers used are shown in Supplementary **Table S8**.

Sequences obtain after mutagenesis procedures are shown in **Table S9**.

DNA sequence of the pET26b containing DERA-MA:

TGGCGAATGGGACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGCGTGACCGCTACACT
TGCCAGCGCCCTAGCGCCCGCTCCTTTCGCTTTCTTCCCTTCCTTTCTCGCCACGTTCGCCGGCTTTCCCCGTCAAGC
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GCATTTGCATGGTTTGTTGAAAACCGGACATGGCACTCCAGTCGCCTTCCCGTTCCGCTATCGGCTGAATTTGATTGC
GAGTGAGATATTTATGCCAGCCAGCCAGACGCAGACGCGCCGAGACAGAACTTAATGGGCCCGCTAACAGCGCGATTT
GCTGGTGACCCAATGCGACCAGATGCTCCACGCCCAGTCGCGTACCGTCTTCATGGGAGAAAATAATACTGTTGATGG
GTGTCTGGTCAGAGACATCAAGAAATAACGCCGGAACATTAGTGCAGGCAGCTTCCACAGCAATGGCATCCTGGTCAT
CCAGCGGATAGTTAATGATCAGCCCACTGACGCGTTGCGCGAGAAGATTGTGCACCGCCGCTTTACAGGCTTCGACGC
CGCTTCGTTCTACCATCGACACCACCACGCTGGCACCCAGTTGATCGGCGCGAGATTTAATCGCCGCGACAATTTGCG
ACGGCGCGTGCAGGGCCAGACTGGAGGTGGCAACGCCAATCAGCAACGACTGTTTGCCCGCCAGTTGTTGTGCCACGC
GGTTGGGAATGTAATTCAGCTCCGCCATCGCCGCTTCCACTTTTTCCCGCGTTTTCGCAGAAACGTGGCTGGCCTGGT
TCACCACGCGGGAAACGGTCTGATAAGAGACACCGGCATACTCTGCGACATCGTATAACGTTACTGGTTTCACATTCA
CCACCCTGAATTGACTCTCTTCCGGGCGCTATCATGCCATACCGCGAAAGGTTTTGCGCCATTCGATGGTGTCCGGGA
TCTCGACGCTCTCCCTTATGCGACTCCTGCATTAGGAAGCAGCCCAGTAGTAGGTTGAGGCCGTTGAGCACCGCCGCC
GCAAGGAATGGTGCATGCAAGGAGATGGCGCCCAACAGTCCCCCGGCCACGGGGCCTGCCACCATACCCACGCCGAAA
CAAGCGCTCATGAGCCCGAAGTGGCGAGCCCGATCTTCCCCATCGGTGATGTCGGCGATATAGGCGCCAGCAACCGCA
CCTGTGGCGCCGGTGATGCCGGCCACGATGCGTCCGGCGTAGAGGATCGAGATCTCGATCCCGCGAAATTAATACGAC
TCACTATAGGGGAATTGTGAGCGGATAACAATTCCCCTCTAGAAATAATTTTGTTTAACTTTAAGAAGGAGATATACA
T**ATGACCGACCTGAAGGCGAGCAGCCTGCGTGCGCTGAAACTGATGGATCTGAGCACCCTGAACGGCGACTACACCGA**
TGAGAAGGTTATCGCGCTGTGCCACCAGGCGAAAACCCCGGTGGGTAACACCGCGGCGATCAGCATTTATCCGCGTAG
CATCCCGATTGCGCGTAAGACCCTGAAAGAGCAAGGCACCCCGGAAATCCGTATTGCGACCGTTACCAACTTCCCGCA
CGGTAACGACGATATCGACATTGCGCTGGCGGAAACCCGTGCGGCGATTGCGTACGGCGCGGACGAAGTGGATGTGGT
TTTCCCGTATCGTGCGCTGATGGCGGGCAACGAGCAGGTTGGTTTTGATCTGGTGAAGGCGTGCAAAGAAGCGTGCGC
GGCGGCGAACGTGCTGCTGAAGGTTATCATTGAGAGCGGTGAACTGAAGGACGAGGCGCTGATCCGTAAAGCGAGCGA
AATCAGCATTAAGGCGGGCGCGGATTTCATTAAAACCAGCACCGGTCTGGTGGCGGTTAACGCGACCCCGGAGAGCGC
GCGTATCATGATGGAAGTTATTCGTGACATGGGCGTGGAAAAGAGCGTTGGTTTTAAAGTGACCGGTGGCGCGCGTAC
CGCGGAGGATGCGCAAAAATACCTGGCGATCGCGGATGAGCTGTTTGGTGCGGACTGGGCGGATGCGCGTCACTATCG
TTTTGGTGCGAGCGGTCTGCTGGCGAGCCTGCTGAAGGCGCTGGGTCACGGCGATGGTAAAAGCGCGAGCAGCTACCT
CGAGCACCACCACCACCACCACTGAGATCCGGCTGCTAACAAAGCCCGAAAGGAAGCTGAGTTGGCTGCTGCCACCGC
TGAGCAATAACTAGCATAACCCCTTGGGGCCTCTAAACGGGTCTTGAGGGGTTTTTTGCTGAAAGGAGGAACTATATC
CGGAT

Procedure A:

Mutagenic primers (**Table S8**, 25 ng μL^{-1}) were used in PCR reactions (50 μL) using 25 ng of the template DNA, dNTP mix, *PfuUltra* HF DNA polymerase (2.5 U) and reaction buffer. PCR parameters were: 1 cycle for 35 seconds at 95 ˚C, following by 16 cycles, each one consisted of 30 seconds at 95 ˚C (denaturation), 1 minute at 55 ˚C (annealing) and 6 minutes at 68˚C (extension). After the PCR, the reactions were treated with DpnI enzyme (10 U) to remove the starting template, following by purification of the products with StrataClean resin provided by the kit. Next, 2 μL of the purified product were used to transform electrocompetent XL1 blue *E.coli* cells. In total, 100 μL of the transformation were plated intro LB-agar petri dishes containing kanamycin (50 μg mL^{-1}) and the next day single colonies were picked. These colonies were used to inoculate LB medium overnight. The resulted overnight cultures were used for plasmid extraction and the mutations introduced were verified with sequencing. After the new sequence was confirmed, the plasmids were used to transform BL21(DE3) competent cells which were used for enzyme expression.

Procedure B:

Mutagenic primers (**Table S8**, 0.5 μM) were used in PCR reactions (25 μL) using 20 ng of the template DNA, and Q5 Hot Start High-Fidelity 2X Master Mix provided by the kit. PCR parameters were: 1 cycle for 30 seconds at 98 ˚C, following by 25 cycles, each one consisted of 10 seconds at 98 ˚C (denaturation), 30 seconds at Ta = Tm + 3 (annealing) and 3 minutes at 72˚C

(extension). After the PCR the reactions were treated with Kinase, Ligase and DpnI (KLD) enzyme mix for circularization and template removal. Next, 5 μL of the purified product were used to transform competent BL21 (DE3) *E.coli* cells. In total, 100 μL of the transformation were plated intro LB-agar petri dishes containing kanamycin (50 μg mL^{-1}) and the next day single colonies were picked. These colonies were used to inoculate LB medium overnight. The resulted overnight cultures were used for plasmid extraction and for glycerol stock preparation. The mutations introduced were verified with sequencing and the glycerol stocks were used for enzyme expression.

Table S8. Primers used for construction of DERA-MA variants. Mutations introduced are shown in bold.

Parental DNA	**Mutations**		**Primer Sequence (5'→ 3')**
DERA-MA	S18A	F	GAAACTGATGGATCTG**gc**CACCCTGAACGGCGAC
		R	GTCGCCGTTCAGGGTG**gc**CAGATCCATCAGTTTC
	S18G	F	GATGGATCTG**g**GCACCCTGAAC
		R	AGTTTCAGCGCACGCAGG
	S18V	F	CTGAAACTGATGGATCTG**gt**CACCCTGAACGGCGACTA
		R	TAGTCGCCGTTCAGGGTG**ac**CAGATCCATCAGTTTCAG
	S238A	F	TTTTGGTGCG**gc**CGGTCTGCTG
		R	CGATAGTGACGCGCATCC
	Y49A	F	CACCGCGGCGATCAGCATT**gc**TCCGCGTAGC
		R	GCTACGCGGA**gc**AATGCTGATCGCCGCGGTG
	K167L	F	GGATTTCATT**ctg**ACCAGCACCGG
		R	GCGCCCGCCTTAATG
	L172A	F	CAGCACCGGT**gc**GGTGGCGGTT
		R	GTTTTAATGAAATCCGCGCCC
	T203A	F	TTTTAAAGTG**g**CCGGTGGCGC
		R	CCAACGCTCTTTTCCACG
	T203V	F	TTTTAAAGTG**gt**CGGTGGCGCG
		R	CCAACGCTCTTTTCCACG
	T203L	F	TTTTAAAGTG**ct**CGGTGGCGCG
		R	CCAACGCTCTTTTCCACG
	T203I	F	TTTTAAAGTG**at**CGGTGGCGCG
		R	CCAACGCTCTTTTCCACG
	Saturation T203	F	TTTTAAAGTG**nnk**GGTGGCGCGCG
		R	CCAACGCTCTTTTCCACG
	Error prone	Fep	TTGTTTAACTTTAAGAAGGAGATATACATATG
		Rep	GGTGGTGGTGCTCGAG
DERA-MA$^{S18A/T203A}$	Saturation A18	F	TAATACGACTCACTATAGGG
		R	TCGCCGTTCAGGGT**mnn**CAGATCCATCAGTTTCAGCG
	Saturation L20	F	GATCTGGCCACC**nnk**AACGGCGACTACACCGAT
		R	TGTAGTCGCCGTT**mnn**GGTGGCCAGATCCATCAG
	Saturation I48	F	GGCGATCAGC**nnk**TATCCGCGTAGCATCC
		R	TACGCGGATA**mnn**GCTGATCGCCGCGGTG
	Saturation Y49	F	TAATACGACTCACTATAGGG
		R	TACGCGG**mnn**AATGCTGATCGCCGCGGTGTTAC
	Saturation F76	F	CGACCGTTACCAAC**nnk**CCGCACGGTAACGACG

		R	GTTACCGTGCGG**mnn**GTTGGTAACGGTCGCAATAC
	Saturation V138	F	CGTGCTGCTGAAG**nnk**ATCATTGAGAGCGGTGAAC
		R	CGCTCTCAATGAT**mnn**CTTCAGCAGCACGTTCGCC
	Saturation I139	F	CGTGCTGCTGAAGGTT**nnk**ATTGAGAGCGGTGAACTGAAG
		R	TTCACCGCTCTCAAT**mnn**AACCTTCAGCAGCACGTTCGC
	Saturation T170	F	TCATTAAAACCAGC**nnk**GGTCTGGTGGCGGTTAACGC
		R	ACCGCCACCAGACC**mnn**GCTGGTTTTAATGAAATCCG
	Saturation G171	F	ATTAAAACCAGCACC**nnk**CTGGTGGCGGTTAACGCGACC
		R	GTTAACCGCCACCAG**mnn**GGTGCTGGTTTTAATGAAATC
	Saturation L172	F	AACCAGCACCGGT**nnk**GTGGCGGTTAACGCGACCC
		R	CGTTAACCGCCAC**mnn**ACCGGTGCTGGTTTTAATG
	Saturation G236	F	CGCGTCACTATCGTTTT**nnk**GCGAGCGGTCTG
		R	GCTCGC**mnn**AAAACGATAGTGACGCGCATCCG
	Saturation S238	F	CGTTTTGGTGCG**nnk**GGTCTGCTGGCGAGCCTG
		R	GCTAGTTATTGCTCAGCGG
	Saturation G239	F	TGGTGCGAGC**nnk**CTGCTGGCGAGCCTGC
		R	GCTAGTTATTGCTCAGCGG
	Saturation S52	F	GCATTTATCCGCGT**nnk**ATCCCGATTGCGCGTAAGAC
		R	GGAAAACCACATCCACTTCGTCCG
	S52Y	F	ATTTATCCGCGT**tat**ATCCCGATTGCGCGTAAG
		R	CGCAATCGGGAT**ata**ACGCGGATAAATGCTGATCG

Table S9. The amino acid and DNA sequences of the enzymes used in this study. Mutations in relation to the parental enzyme DERA-MA are shown in bold.

Enzyme	Sequence
DERA-MA	MTDLKASSLRALKLMDLSTLNGDYTDEKVIALCHQAKTPVGNTAAISIYPRSIPIARKTLKEQGT PEIRIATVTNFPHGNDDIDIALAETRAAIAYGADEVDVVFPYRALMAGNEQVGFDLVKACKEACA AANVLLKVIIESGELKDEALIRKASEISIKAGADFIKTSTGLVAVNATPESARIMMEVIRDMGVE KSVGFKVTGGARTAEDAQKYLAIADELFGADWADARHYRFGASGLLASLLKALGHGDGKSASSYL EHHHHHH
	ATGACCGACCTGAAGGCGAGCAGCCTGCGTGCGCTGAAACTGATGGATCTGAGCACCCTGAACGG CGACTACACCGATGAGAAGGTTATCGCGCTGTGCCACCAGGCGAAAACCCCGGTGGGTAACACCG CGGCGATCAGCATTTATCCGCGTAGCATCCCGATTGCGCGTAAGACCCTGAAAGAGCAAGGCACC CCGGAAATCCGTATTGCGACCGTTACCAACTTCCCGCACGGTAACGACGATATCGACATTGCGCT GGCGGAAACCCGTGCGGCGATTGCGTACGGCGCGGACGAAGTGGATGTGGTTTTCCCGTATCGTG CGCTGATGGCGGGCAACGAGCAGGTTGGTTTTGATCTGGTGAAGGCGTGCAAAGAAGCGTGCGCG GCGGCGAACGTGCTGCTGAAGGTTATCATTGAGAGCGGTGAACTGAAGGACGAGGCGCTGATCCG TAAAGCGAGCGAAATCAGCATTAAGGCGGGCGCGGATTTCATTAAAACCAGCACCGGTCTGGTGG CGGTTAACGCGACCCCGGAGAGCGCGCGTATCATGATGGAAGTTATTCGTGACATGGGCGTGGAA AAGAGCGTTGGTTTTAAAGTGACCGGTGGCGCGCGTACCGCGGAGGATGCGCAAAAATACCTGGC GATCGCGGATGAGCTGTTTGGTGCGGACTGGGCGGATGCGCGTCACTATCGTTTTGGTGCGAGCG GTCTGCTGGCGAGCCTGCTGAAGGCGCTGGGTCACGGCGATGGTAAAAGCGCGAGCAGCTACCTC GAGCACCACCACCACCACCAC
DERA-MA^{S18A}	MTDLKASSLRALKLMDL**A**TLNGDYTDEKVIALCHQAKTPVGNTAAISIYPRSIPIARKTLKEQGT PEIRIATVTNFPHGNDDIDIALAETRAAIAYGADEVDVVFPYRALMAGNEQVGFDLVKACKEACA AANVLLKVIIESGELKDEALIRKASEISIKAGADFIKTSTGLVAVNATPESARIMMEVIRDMGVE KSVGFKVTGGARTAEDAQKYLAIADELFGADWADARHYRFGASGLLASLLKALGHGDGKSASSYL EHHHHHH
	ATGACCGACCTGAAGGCGAGCAGCCTGCGTGCGCTGAAACTGATGGATCTG**GCC**ACCCTGAACGG CGACTACACCGATGAGAAGGTTATCGCGCTGTGCCACCAGGCGAAAACCCCGGTGGGTAACACCG CGGCGATCAGCATTTATCCGCGTAGCATCCCGATTGCGCGTAAGACCCTGAAAGAGCAAGGCACC CCGGAAATCCGTATTGCGACCGTTACCAACTTCCCGCACGGTAACGACGATATCGACATTGCGCT GGCGGAAACCCGTGCGGCGATTGCGTACGGCGCGGACGAAGTGGATGTGGTTTTCCCGTATCGTG CGCTGATGGCGGGCAACGAGCAGGTTGGTTTTGATCTGGTGAAGGCGTGCAAAGAAGCGTGCGCG GCGGCGAACGTGCTGCTGAAGGTTATCATTGAGAGCGGTGAACTGAAGGACGAGGCGCTGATCCG TAAAGCGAGCGAAATCAGCATTAAGGCGGGCGCGGATTTCATTAAAACCAGCACCGGTCTGGTGG CGGTTAACGCGACCCCGGAGAGCGCGCGTATCATGATGGAAGTTATTCGTGACATGGGCGTGGAA AAGAGCGTTGGTTTTAAAGTGACCGGTGGCGCGCGTACCGCGGAGGATGCGCAAAAATACCTGGC GATCGCGGATGAGCTGTTTGGTGCGGACTGGGCGGATGCGCGTCACTATCGTTTTGGTGCGAGCG GTCTGCTGGCGAGCCTGCTGAAGGCGCTGGGTCACGGCGATGGTAAAAGCGCGAGCAGCTACCTC GAGCACCACCACCACCACCAC
DERA-MA^{S18G}	MTDLKASSLRALKLMDL**G**TLNGDYTDEKVIALCHQAKTPVGNTAAISIYPRSIPIARKTLKEQGT PEIRIATVTNFPHGNDDIDIALAETRAAIAYGADEVDVVFPYRALMAGNEQVGFDLVKACKEACA AANVLLKVIIESGELKDEALIRKASEISIKAGADFIKTSTGLVAVNATPESARIMMEVIRDMGVE KSVGFKVTGGARTAEDAQKYLAIADELFGADWADARHYRFGASGLLASLLKALGHGDGKSASSYL EHHHHHH
	ATGACCGACCTGAAGGCGAGCAGCCTGCGTGCGCTGAAACTGATGGATCTG**GGC**ACCCTGAACGG CGACTACACCGATGAGAAGGTTATCGCGCTGTGCCACCAGGCGAAAACCCCGGTGGGTAACACCG CGGCGATCAGCATTTATCCGCGTAGCATCCCGATTGCGCGTAAGACCCTGAAAGAGCAAGGCACC CCGGAAATCCGTATTGCGACCGTTACCAACTTCCCGCACGGTAACGACGATATCGACATTGCGCT GGCGGAAACCCGTGCGGCGATTGCGTACGGCGCGGACGAAGTGGATGTGGTTTTCCCGTATCGTG CGCTGATGGCGGGCAACGAGCAGGTTGGTTTTGATCTGGTGAAGGCGTGCAAAGAAGCGTGCGCG GCGGCGAACGTGCTGCTGAAGGTTATCATTGAGAGCGGTGAACTGAAGGACGAGGCGCTGATCCG TAAAGCGAGCGAAATCAGCATTAAGGCGGGCGCGGATTTCATTAAAACCAGCACCGGTCTGGTGG CGGTTAACGCGACCCCGGAGAGCGCGCGTATCATGATGGAAGTTATTCGTGACATGGGCGTGGAA AAGAGCGTTGGTTTTAAAGTGACCGGTGGCGCGCGTACCGCGGAGGATGCGCAAAAATACCTGGC GATCGCGGATGAGCTGTTTGGTGCGGACTGGGCGGATGCGCGTCACTATCGTTTTGGTGCGAGCG GTCTGCTGGCGAGCCTGCTGAAGGCGCTGGGTCACGGCGATGGTAAAAGCGCGAGCAGCTACCTC GAGCACCACCACCACCACCAC

DERA-MA^{S18V}	MTDLKASSLRALKLMDL**V**TLNGDYTDEKVIALCHQAKTPVGNTAAISIYPRSIPIARKTLKEQGT PEIRIATVTNFPHGNDDIDIALAETRAAIAYGADEVDVVFPYRALMAGNEQVGFDLVKACKEACA AANVLLKVIIESGELKDEALIRKASEISIKAGADFIKTSTGLVAVNATPESARIMMEVIRDMGVE KSVGFKVTGGARTAEDAQKYLAIADELFGADWADARHYRFGASGLLASLLKALGHGDGKSASSYL EHHHHHH
	ATGACCGACCTGAAGGCGAGCAGCCTGCGTGCGCTGAAACTGATGGATCTG**GTC**ACCCTGAACGG CGACTACACCGATGAGAAGGTTATCGCGCTGTGCCACCAGGCGAAAACCCCGGTGGGTAACACCG CGGCGATCAGCATTTATCCGCGTAGCATCCCGATTGCGCGTAAGACCCTGAAAGAGCAAGGCACC CCGGAAATCCGTATTGCGACCGTTACCAACTTCCCGCACGGTAACGACGATATCGACATTGCGCT GGCGGAAACCCGTGCGGCGATTGCGTACGGCGCGGACGAAGTGGATGTGGTTTTCCCGTATCGTG CGCTGATGGCGGGCAACGAGCAGGTTGGTTTTGATCTGGTGAAGGCGTGCAAAGAAGCGTGCGCG GCGGCGAACGTGCTGCTGAAGGTTATCATTGAGAGCGGTGAACTGAAGGACGAGGCGCTGATCCG TAAAGCGAGCGAAATCAGCATTAAGGCGGGCGCGGATTTCATTAAAACCAGCACCGGTCTGGTGG CGGTTAACGCGACCCCGGAGAGCGCGCGTATCATGATGGAAGTTATTCGTGACATGGGCGTGGAA AAGAGCGTTGGTTTTAAAGTGACCGGTGGCGCGCGTACCGCGGAGGATGCGCAAAAATACCTGGC GATCGCGGATGAGCTGTTTGGTGCGGACTGGGCGGATGCGCGTCACTATCGTTTTGGTGCGAGCG GTCTGCTGGCGAGCCTGCTGAAGGCGCTGGGTCACGGCGATGGTAAAAGCGCGAGCAGCTACCTC GAGCACCACCACCACCACCAC
DERA-MA^{S238A}	MTDLKASSLRALKLMDLSTLNGDYTDEKVIALCHQAKTPVGNTAAISIYPRSIPIARKTLKEQGT PEIRIATVTNFPHGNDDIDIALAETRAAIAYGADEVDVVFPYRALMAGNEQVGFDLVKACKEACA AANVLLKVIIESGELKDEALIRKASEISIKAGADFIKTSTGLVAVNATPESARIMMEVIRDMGVE KSVGFKVTGGARTAEDAQKYLAIADELFGADWADARHYRFGA**A**GLLASLLKALGHGDGKSASSYL EHHHHHH
	ATGACCGACCTGAAGGCGAGCAGCCTGCGTGCGCTGAAACTGATGGATCTGAGCACCCTGAACGG CGACTACACCGATGAGAAGGTTATCGCGCTGTGCCACCAGGCGAAAACCCCGGTGGGTAACACCG CGGCGATCAGCATTTATCCGCGTAGCATCCCGATTGCGCGTAAGACCCTGAAAGAGCAAGGCACC CCGGAAATCCGTATTGCGACCGTTACCAACTTCCCGCACGGTAACGACGATATCGACATTGCGCT GGCGGAAACCCGTGCGGCGATTGCGTACGGCGCGGACGAAGTGGATGTGGTTTTCCCGTATCGTG CGCTGATGGCGGGCAACGAGCAGGTTGGTTTTGATCTGGTGAAGGCGTGCAAAGAAGCGTGCGCG GCGGCGAACGTGCTGCTGAAGGTTATCATTGAGAGCGGTGAACTGAAGGACGAGGCGCTGATCCG TAAAGCGAGCGAAATCAGCATTAAGGCGGGCGCGGATTTCATTAAAACCAGCACCGGTCTGGTGG CGGTTAACGCGACCCCGGAGAGCGCGCGTATCATGATGGAAGTTATTCGTGACATGGGCGTGGAA AAGAGCGTTGGTTTTAAAGTGACCGGTGGCGCGCGTACCGCGGAGGATGCGCAAAAATACCTGGC GATCGCGGATGAGCTGTTTGGTGCGGACTGGGCGGATGCGCGTCACTATCGTTTTGGTGCG**GCC**G GTCTGCTGGCGAGCCTGCTGAAGGCGCTGGGTCACGGCGATGGTAAAAGCGCGAGCAGCTACCTC GAGCACCACCACCACCACCAC
DERA-MA^{Y49A}	MTDLKASSLRALKLMDLSTLNGDYTDEKVIALCHQAKTPVGNTAAISI**A**PRSIPIARKTLKEQGT PEIRIATVTNFPHGNDDIDIALAETRAAIAYGADEVDVVFPYRALMAGNEQVGFDLVKACKEACA AANVLLKVIIESGELKDEALIRKASEISIKAGADFIKTSTGLVAVNATPESARIMMEVIRDMGVE KSVGFKVTGGARTAEDAQKYLAIADELFGADWADARHYRFGASGLLASLLKALGHGDGKSASSYL EHHHHHH
	ATGACCGACCTGAAGGCGAGCAGCCTGCGTGCGCTGAAACTGATGGATCTGAGCACCCTGAACGG CGACTACACCGATGAGAAGGTTATCGCGCTGTGCCACCAGGCGAAAACCCCGGTGGGTAACACCG CGGCGATCAGCATT**GCT**CCGCGTAGCATCCCGATTGCGCGTAAGACCCTGAAAGAGCAAGGCACC CCGGAAATCCGTATTGCGACCGTTACCAACTTCCCGCACGGTAACGACGATATCGACATTGCGCT GGCGGAAACCCGTGCGGCGATTGCGTACGGCGCGGACGAAGTGGATGTGGTTTTCCCGTATCGTG CGCTGATGGCGGGCAACGAGCAGGTTGGTTTTGATCTGGTGAAGGCGTGCAAAGAAGCGTGCGCG GCGGCGAACGTGCTGCTGAAGGTTATCATTGAGAGCGGTGAACTGAAGGACGAGGCGCTGATCCG TAAAGCGAGCGAAATCAGCATTAAGGCGGGCGCGGATTTCATTAAAACCAGCACCGGTCTGGTGG CGGTTAACGCGACCCCGGAGAGCGCGCGTATCATGATGGAAGTTATTCGTGACATGGGCGTGGAA AAGAGCGTTGGTTTTAAAGTGACCGGTGGCGCGCGTACCGCGGAGGATGCGCAAAAATACCTGGC GATCGCGGATGAGCTGTTTGGTGCGGACTGGGCGGATGCGCGTCACTATCGTTTTGGTGCGAGCG GTCTGCTGGCGAGCCTGCTGAAGGCGCTGGGTCACGGCGATGGTAAAAGCGCGAGCAGCTACCTC GAGCACCACCACCACCACCAC
DERA-MA^{L172A}	MTDLKASSLRALKLMDLSTLNGDYTDEKVIALCHQAKTPVGNTAAISIYPRSIPIARKTLKEQGT PEIRIATVTNFPHGNDDIDIALAETRAAIAYGADEVDVVFPYRALMAGNEQVGFDLVKACKEACA AANVLLKVIIESGELKDEALIRKASEISIKAGADFIKTSTG**A**VAVNATPESARIMMEVIRDMGVE KSVGFKVTGGARTAEDAQKYLAIADELFGADWADARHYRFGASGLLASLLKALGHGDGKSASSYL EHHHHHH

	ATGACCGACCTGAAGGCGAGCAGCCTGCGTGCGCTGAAACTGATGGATCTGAGCACCCTGAACGG CGACTACACCGATGAGAAGGTTATCGCGCTGTGCCACCAGGCGAAAACCCCGGTGGGTAACACCG CGGCGATCAGCATTTATCCGCGTAGCATCCCGATTGCGCGTAAGACCCTGAAAGAGCAAGGCACC CCGGAAATCCGTATTGCGACCGTTACCAACTTCCCGCACGGTAACGACGATATCGACATTGCGCT GGCGGAAACCCGTGCGGCGATTGCGTACGGCGCGGACGAAGTGGATGTGGTTTTCCCGTATCGTG CGCTGATGGCGGGCAACGAGCAGGTTGGTTTTGATCTGGTGAAGGCGTGCAAAGAAGCGTGCGCG GCGGCGAACGTGCTGCTGAAGGTTATCATTGAGAGCGGTGAACTGAAGGACGAGGCGCTGATCCG TAAAGCGAGCGAAATCAGCATTAAGGCGGGCGCGGATTTCATTAAAACCAGCACCGGT**GCG**GTGG CGGTTAACGCGACCCCGGAGAGCGCGCGTATCATGATGGAAGTTATTCGTGACATGGGCGTGGAA AAGAGCGTTGGTTTTAAAGTGACCGGTGGCGCGCGTACCGCGGAGGATGCGCAAAAATACCTGGC GATCGCGGATGAGCTGTTTGGTGCGGACTGGGCGGATGCGCGTCACTATCGTTTTGGTGCGAGCG GTCTGCTGGCGAGCCTGCTGAAGGCGCTGGGTCACGGCGATGGTAAAAGCGCGAGCAGCTACCTC GAGCACCACCACCACCACCAC
DERA-MA^{T203A}	MTDLKASSLRALKLMDLSTLNGDYTDEKVIALCHQAKTPVGNTAAISIYPRSIPIARKTLKEQGT PEIRIATVTNFPHGNDDIDIALAETRAAIAYGADEVDVVFPYRALMAGNEQVGFDLVKACKEACA AANVLLKVIIESGELKDEALIRKASEISIKAGADFIKTSTGLVAVNATPESARIMMEVIRDMGVE KSVGFKV**A**GGARTAEDAQKYLAIADELFGADWADARHYRFGASGLLASLLKALGHGDGKSASSYL EHHHHHH
	ATGACCGACCTGAAGGCGAGCAGCCTGCGTGCGCTGAAACTGATGGATCTGAGCACCCTGAACGG CGACTACACCGATGAGAAGGTTATCGCGCTGTGCCACCAGGCGAAAACCCCGGTGGGTAACACCG CGGCGATCAGCATTTATCCGCGTAGCATCCCGATTGCGCGTAAGACCCTGAAAGAGCAAGGCACC CCGGAAATCCGTATTGCGACCGTTACCAACTTCCCGCACGGTAACGACGATATCGACATTGCGCT GGCGGAAACCCGTGCGGCGATTGCGTACGGCGCGGACGAAGTGGATGTGGTTTTCCCGTATCGTG CGCTGATGGCGGGCAACGAGCAGGTTGGTTTTGATCTGGTGAAGGCGTGCAAAGAAGCGTGCGCG GCGGCGAACGTGCTGCTGAAGGTTATCATTGAGAGCGGTGAACTGAAGGACGAGGCGCTGATCCG TAAAGCGAGCGAAATCAGCATTAAGGCGGGCGCGGATTTCATTAAAACCAGCACCGGTCTGGTGG CGGTTAACGCGACCCCGGAGAGCGCGCGTATCATGATGGAAGTTATTCGTGACATGGGCGTGGAA AAGAGCGTTGGTTTTAAAGTG**GCC**GGTGGCGCGCGTACCGCGGAGGATGCGCAAAAATACCTGGC GATCGCGGATGAGCTGTTTGGTGCGGACTGGGCGGATGCGCGTCACTATCGTTTTGGTGCGAGCG GTCTGCTGGCGAGCCTGCTGAAGGCGCTGGGTCACGGCGATGGTAAAAGCGCGAGCAGCTACCTC GAGCACCACCACCACCACCAC
DERA-MA^{K167L}	MTDLKASSLRALKLMDLSTLNGDYTDEKVIALCHQAKTPVGNTAAISIYPRSIPIARKTLKEQGT PEIRIATVTNFPHGNDDIDIALAETRAAIAYGADEVDVVFPYRALMAGNEQVGFDLVKACKEACA AANVLLKVIIESGELKDEALIRKASEISIKAGADFI**L**TSTGLVAVNATPESARIMMEVIRDMGVE KSVGFKVTGGARTAEDAQKYLAIADELFGADWADARHYRFGASGLLASLLKALGHGDGKSASSYL EHHHHHH
	ATGACCGACCTGAAGGCGAGCAGCCTGCGTGCGCTGAAACTGATGGATCTGAGCACCCTGAACGG CGACTACACCGATGAGAAGGTTATCGCGCTGTGCCACCAGGCGAAAACCCCGGTGGGTAACACCG CGGCGATCAGCATTTATCCGCGTAGCATCCCGATTGCGCGTAAGACCCTGAAAGAGCAAGGCACC CCGGAAATCCGTATTGCGACCGTTACCAACTTCCCGCACGGTAACGACGATATCGACATTGCGCT GGCGGAAACCCGTGCGGCGATTGCGTACGGCGCGGACGAAGTGGATGTGGTTTTCCCGTATCGTG CGCTGATGGCGGGCAACGAGCAGGTTGGTTTTGATCTGGTGAAGGCGTGCAAAGAAGCGTGCGCG GCGGCGAACGTGCTGCTGAAGGTTATCATTGAGAGCGGTGAACTGAAGGACGAGGCGCTGATCCG TAAAGCGAGCGAAATCAGCATTAAGGCGGGCGCGGATTTCATT**CTG**ACCAGCACCGGTCTGGTGG CGGTTAACGCGACCCCGGAGAGCGCGCGTATCATGATGGAAGTTATTCGTGACATGGGCGTGGAA AAGAGCGTTGGTTTTAAAGTGACCGGTGGCGCGCGTACCGCGGAGGATGCGCAAAAATACCTGGC GATCGCGGATGAGCTGTTTGGTGCGGACTGGGCGGATGCGCGTCACTATCGTTTTGGTGCGAGCG GTCTGCTGGCGAGCCTGCTGAAGGCGCTGGGTCACGGCGATGGTAAAAGCGCGAGCAGCTACCTC GAGCACCACCACCACCACCAC
DERA-MA$^{S18A/T203A}$	MTDLKASSLRALKLMDL**A**TLNGDYTDEKVIALCHQAKTPVGNTAAISIYPRSIPIARKTLKEQGT PEIRIATVTNFPHGNDDIDIALAETRAAIAYGADEVDVVFPYRALMAGNEQVGFDLVKACKEACA AANVLLKVIIESGELKDEALIRKASEISIKAGADFIKTSTGLVAVNATPESARIMMEVIRDMGVE KSVGFKV**A**GGARTAEDAQKYLAIADELFGADWADARHYRFGASGLLASLLKALGHGDGKSASSYL EHHHHHH
	ATGACCGACCTGAAGGCGAGCAGCCTGCGTGCGCTGAAACTGATGGATCTG**GCC**ACCCTGAACGG CGACTACACCGATGAGAAGGTTATCGCGCTGTGCCACCAGGCGAAAACCCCGGTGGGTAACACCG CGGCGATCAGCATTTATCCGCGTAGCATCCCGATTGCGCGTAAGACCCTGAAAGAGCAAGGCACC CCGGAAATCCGTATTGCGACCGTTACCAACTTCCCGCACGGTAACGACGATATCGACATTGCGCT GGCGGAAACCCGTGCGGCGATTGCGTACGGCGCGGACGAAGTGGATGTGGTTTTCCCGTATCGTG

	CGCTGATGGCGGGCAACGAGCAGGTTGGTTTTGATCTGGTGAAGGCGTGCAAAGAAGCGTGCGCG GCGGCGAACGTGCTGCTGAAGGTTATCATTGAGAGCGGTGAACTGAAGGACGAGGCGCTGATCCG TAAAGCGAGCGAAATCAGCATTAAGGCGGGCGCGGATTTCATTAAAACCAGCACCGGTCTGGTGG CGGTTAACGCGACCCCGGAGAGCGCGCGTATCATGATGGAAGTTATTCGTGACATGGGCGTGGAA AAGAGCGTTGGTTTTAAAGTG**GCC**GGTGGCGCGCGTACCGCGGAGGATGCGCAAAAATACCTGGC GATCGCGGATGAGCTGTTTGGTGCGGACTGGGCGGATGCGCGTCACTATCGTTTTGGTGCGAGCG GTCTGCTGGCGAGCCTGCTGAAGGCGCTGGGTCACGGCGATGGTAAAAGCGCGAGCAGCTACCTC GAGCACCACCACCACCACCAC
DERA-MA$^{S18A/T203V}$	MTDLKASSLRALKLMDL**A**TLNGDYTDEKVIALCHQAKTPVGNTAAISIYPRSIPIARKTLKEQGT PEIRIATVTNFPHGNDDIDIALAETRAAIAYGADEVDVVFPYRALMAGNEQVGFDLVKACKEACA AANVLLKVIIESGELKDEALIRKASEISIKAGADFIKTSTGLVAVNATPESARIMMEVIRDMGVE KSVGFKV**V**GGARTAEDAQKYLAIADELFGADWADARHYRFGASGLLASLLKALGHGDGKSASSYL EHHHHHH
	ATGACCGACCTGAAGGCGAGCAGCCTGCGTGCGCTGAAACTGATGGATCTG**GCC**ACCCTGAACGG CGACTACACCGATGAGAAGGTTATCGCGCTGTGCCACCAGGCGAAAACCCCGGTGGGTAACACCG CGGCGATCAGCATTTATCCGCGTAGCATCCCGATTGCGCGTAAGACCCTGAAAGAGCAAGGCACC CCGGAAATCCGTATTGCGACCGTTACCAACTTCCCGCACGGTAACGACGATATCGACATTGCGCT GGCGGAAACCCGTGCGGCGATTGCGTACGGCGCGGACGAAGTGGATGTGGTTTTCCCGTATCGTG CGCTGATGGCGGGCAACGAGCAGGTTGGTTTTGATCTGGTGAAGGCGTGCAAAGAAGCGTGCGCG GCGGCGAACGTGCTGCTGAAGGTTATCATTGAGAGCGGTGAACTGAAGGACGAGGCGCTGATCCG TAAAGCGAGCGAAATCAGCATTAAGGCGGGCGCGGATTTCATTAAAACCAGCACCGGTCTGGTGG CGGTTAACGCGACCCCGGAGAGCGCGCGTATCATGATGGAAGTTATTCGTGACATGGGCGTGGAA AAGAGCGTTGGTTTTAAAGTG**GTC**GGTGGCGCGCGTACCGCGGAGGATGCGCAAAAATACCTGGC GATCGCGGATGAGCTGTTTGGTGCGGACTGGGCGGATGCGCGTCACTATCGTTTTGGTGCGAGCG GTCTGCTGGCGAGCCTGCTGAAGGCGCTGGGTCACGGCGATGGTAAAAGCGCGAGCAGCTACCTC GAGCACCACCACCACCACCAC
DERA-MA$^{S18A/T203L}$	MTDLKASSLRALKLMDL**A**TLNGDYTDEKVIALCHQAKTPVGNTAAISIYPRSIPIARKTLKEQGT PEIRIATVTNFPHGNDDIDIALAETRAAIAYGADEVDVVFPYRALMAGNEQVGFDLVKACKEACA AANVLLKVIIESGELKDEALIRKASEISIKAGADFIKTSTGLVAVNATPESARIMMEVIRDMGVE KSVGFKV**L**GGARTAEDAQKYLAIADELFGADWADARHYRFGASGLLASLLKALGHGDGKSASSYL EHHHHHH
	ATGACCGACCTGAAGGCGAGCAGCCTGCGTGCGCTGAAACTGATGGATCTG**GCC**ACCCTGAACGG CGACTACACCGATGAGAAGGTTATCGCGCTGTGCCACCAGGCGAAAACCCCGGTGGGTAACACCG CGGCGATCAGCATTTATCCGCGTAGCATCCCGATTGCGCGTAAGACCCTGAAAGAGCAAGGCACC CCGGAAATCCGTATTGCGACCGTTACCAACTTCCCGCACGGTAACGACGATATCGACATTGCGCT GGCGGAAACCCGTGCGGCGATTGCGTACGGCGCGGACGAAGTGGATGTGGTTTTCCCGTATCGTG CGCTGATGGCGGGCAACGAGCAGGTTGGTTTTGATCTGGTGAAGGCGTGCAAAGAAGCGTGCGCG GCGGCGAACGTGCTGCTGAAGGTTATCATTGAGAGCGGTGAACTGAAGGACGAGGCGCTGATCCG TAAAGCGAGCGAAATCAGCATTAAGGCGGGCGCGGATTTCATTAAAACCAGCACCGGTCTGGTGG CGGTTAACGCGACCCCGGAGAGCGCGCGTATCATGATGGAAGTTATTCGTGACATGGGCGTGGAA AAGAGCGTTGGTTTTAAAGTG**CTC**GGTGGCGCGCGTACCGCGGAGGATGCGCAAAAATACCTGGC GATCGCGGATGAGCTGTTTGGTGCGGACTGGGCGGATGCGCGTCACTATCGTTTTGGTGCGAGCG GTCTGCTGGCGAGCCTGCTGAAGGCGCTGGGTCACGGCGATGGTAAAAGCGCGAGCAGCTACCTC GAGCACCACCACCACCACCAC
DERA-MA$^{S18A/T203I}$	MTDLKASSLRALKLMDL**A**TLNGDYTDEKVIALCHQAKTPVGNTAAISIYPRSIPIARKTLKEQGT PEIRIATVTNFPHGNDDIDIALAETRAAIAYGADEVDVVFPYRALMAGNEQVGFDLVKACKEACA AANVLLKVIIESGELKDEALIRKASEISIKAGADFIKTSTGLVAVNATPESARIMMEVIRDMGVE KSVGFKV**I**GGARTAEDAQKYLAIADELFGADWADARHYRFGASGLLASLLKALGHGDGKSASSYL EHHHHHH
	ATGACCGACCTGAAGGCGAGCAGCCTGCGTGCGCTGAAACTGATGGATCTG**GCC**ACCCTGAACGG CGACTACACCGATGAGAAGGTTATCGCGCTGTGCCACCAGGCGAAAACCCCGGTGGGTAACACCG CGGCGATCAGCATTTATCCGCGTAGCATCCCGATTGCGCGTAAGACCCTGAAAGAGCAAGGCACC CCGGAAATCCGTATTGCGACCGTTACCAACTTCCCGCACGGTAACGACGATATCGACATTGCGCT GGCGGAAACCCGTGCGGCGATTGCGTACGGCGCGGACGAAGTGGATGTGGTTTTCCCGTATCGTG CGCTGATGGCGGGCAACGAGCAGGTTGGTTTTGATCTGGTGAAGGCGTGCAAAGAAGCGTGCGCG GCGGCGAACGTGCTGCTGAAGGTTATCATTGAGAGCGGTGAACTGAAGGACGAGGCGCTGATCCG TAAAGCGAGCGAAATCAGCATTAAGGCGGGCGCGGATTTCATTAAAACCAGCACCGGTCTGGTGG CGGTTAACGCGACCCCGGAGAGCGCGCGTATCATGATGGAAGTTATTCGTGACATGGGCGTGGAA AAGAGCGTTGGTTTTAAAGTG**ATC**GGTGGCGCGCGTACCGCGGAGGATGCGCAAAAATACCTGGC

	GATCGCGGATGAGCTGTTTGGTGCGGACTGGGCGGATGCGCGTCACTATCGTTTTGGTGCGAGCG GTCTGCTGGCGAGCCTGCTGAAGGCGCTGGGTCACGGCGATGGTAAAAGCGCGAGCAGCTACCTC GAGCACCACCACCACCACCAC
DERA-MA$^{S18A/S238A}$	MTDLKASSLRALKLMDL**A**TLNGDYTDEKVIALCHQAKTPVGNTAAISIYPRSIPIARKTLKEQGT PEIRIATVTNFPHGNDDIDIALAETRAAIAYGADEVDVVFPYRALMAGNEQVGFDLVKACKEACA AANVLLKVIIESGELKDEALIRKASEISIKAGADFIKTSTGLVAVNATPESARIMMEVIRDMGVE KSVGFKVTGGARTAEDAQKYLAIADELFGADWADARHYRFGA**A**GLLASLLKALGHGDGKSASSYL EHHHHHH
	ATGACCGACCTGAAGGCGAGCAGCCTGCGTGCGCTGAAACTGATGGATCTG**GCC**ACCCTGAACGG CGACTACACCGATGAGAAGGTTATCGCGCTGTGCCACCAGGCGAAAACCCCGGTGGGTAACACCG CGGCGATCAGCATTTATCCGCGTAGCATCCCGATTGCGCGTAAGACCCTGAAAGAGCAAGGCACC CCGGAAATCCGTATTGCGACCGTTACCAACTTCCCGCACGGTAACGACGATATCGACATTGCGCT GGCGGAAACCCGTGCGGCGATTGCGTACGGCGCGGACGAAGTGGATGTGGTTTTCCCGTATCGTG CGCTGATGGCGGGCAACGAGCAGGTTGGTTTTGATCTGGTGAAGGCGTGCAAAGAAGCGTGCGCG GCGGCGAACGTGCTGCTGAAGGTTATCATTGAGAGCGGTGAACTGAAGGACGAGGCGCTGATCCG TAAAGCGAGCGAAATCAGCATTAAGGCGGGCGCGGATTTCATTAAAACCAGCACCGGTCTGGTGG CGGTTAACGCGACCCCGGAGAGCGCGCGTATCATGATGGAAGTTATTCGTGACATGGGCGTGGAA AAGAGCGTTGGTTTTAAAGTGACCGGTGGCGCGCGTACCGCGGAGGATGCGCAAAAATACCTGGC GATCGCGGATGAGCTGTTTGGTGCGGACTGGGCGGATGCGCGTCACTATCGTTTTGGTGCG**GCC**G GTCTGCTGGCGAGCCTGCTGAAGGCGCTGGGTCACGGCGATGGTAAAAGCGCGAGCAGCTACCTC GAGCACCACCACCACCACCAC
DERA-MA$^{S18A/T203A/S238A}$	MTDLKASSLRALKLMDL**A**TLNGDYTDEKVIALCHQAKTPVGNTAAISIYPRSIPIARKTLKEQGT PEIRIATVTNFPHGNDDIDIALAETRAAIAYGADEVDVVFPYRALMAGNEQVGFDLVKACKEACA AANVLLKVIIESGELKDEALIRKASEISIKAGADFIKTSTGLVAVNATPESARIMMEVIRDMGVE KSVGFKV**A**GGARTAEDAQKYLAIADELFGADWADARHYRFGA**A**GLLASLLKALGHGDGKSASSYL EHHHHHH
	ATGACCGACCTGAAGGCGAGCAGCCTGCGTGCGCTGAAACTGATGGATCTG**GCC**ACCCTGAACGG CGACTACACCGATGAGAAGGTTATCGCGCTGTGCCACCAGGCGAAAACCCCGGTGGGTAACACCG CGGCGATCAGCATTTATCCGCGTAGCATCCCGATTGCGCGTAAGACCCTGAAAGAGCAAGGCACC CCGGAAATCCGTATTGCGACCGTTACCAACTTCCCGCACGGTAACGACGATATCGACATTGCGCT GGCGGAAACCCGTGCGGCGATTGCGTACGGCGCGGACGAAGTGGATGTGGTTTTCCCGTATCGTG CGCTGATGGCGGGCAACGAGCAGGTTGGTTTTGATCTGGTGAAGGCGTGCAAAGAAGCGTGCGCG GCGGCGAACGTGCTGCTGAAGGTTATCATTGAGAGCGGTGAACTGAAGGACGAGGCGCTGATCCG TAAAGCGAGCGAAATCAGCATTAAGGCGGGCGCGGATTTCATTAAAACCAGCACCGGTCTGGTGG CGGTTAACGCGACCCCGGAGAGCGCGCGTATCATGATGGAAGTTATTCGTGACATGGGCGTGGAA AAGAGCGTTGGTTTTAAAGTG**GCC**GGTGGCGCGCGTACCGCGGAGGATGCGCAAAAATACCTGGC GATCGCGGATGAGCTGTTTGGTGCGGACTGGGCGGATGCGCGTCACTATCGTTTTGGTGCG**GCC**G GTCTGCTGGCGAGCCTGCTGAAGGCGCTGGGTCACGGCGATGGTAAAAGCGCGAGCAGCTACCTC GAGCACCACCACCACCACCAC
DERA-MA$^{S18A/T203A/G239N}$	MTDLKASSLRALKLMDL**A**TLNGDYTDEKVIALCHQAKTPVGNTAAISIYPRSIPIARKTLKEQGT PEIRIATVTNFPHGNDDIDIALAETRAAIAYGADEVDVVFPYRALMAGNEQVGFDLVKACKEACA AANVLLKVIIESGELKDEALIRKASEISIKAGADFIKTSTGLVAVNATPESARIMMEVIRDMGVE KSVGFKV**A**GGARTAEDAQKYLAIADELFGADWADARHYRFGAS**N**LLASLLKALGHGDGKSASSYL EHHHHHH
	ATGACCGACCTGAAGGCGAGCAGCCTGCGTGCGCTGAAACTGATGGATCTG**GCC**ACCCTGAACGG CGACTACACCGATGAGAAGGTTATCGCGCTGTGCCACCAGGCGAAAACCCCGGTGGGTAACACCG CGGCGATCAGCATTTATCCGCGTAGCATCCCGATTGCGCGTAAGACCCTGAAAGAGCAAGGCACC CCGGAAATCCGTATTGCGACCGTTACCAACTTCCCGCACGGTAACGACGATATCGACATTGCGCT GGCGGAAACCCGTGCGGCGATTGCGTACGGCGCGGACGAAGTGGATGTGGTTTTCCCGTATCGTG CGCTGATGGCGGGCAACGAGCAGGTTGGTTTTGATCTGGTGAAGGCGTGCAAAGAAGCGTGCGCG GCGGCGAACGTGCTGCTGAAGGTTATCATTGAGAGCGGTGAACTGAAGGACGAGGCGCTGATCCG TAAAGCGAGCGAAATCAGCATTAAGGCGGGCGCGGATTTCATTAAAACCAGCACCGGTCTGGTGG CGGTTAACGCGACCCCGGAGAGCGCGCGTATCATGATGGAAGTTATTCGTGACATGGGCGTGGAA AAGAGCGTTGGTTTTAAAGTG**GCC**GGTGGCGCGCGTACCGCGGAGGATGCGCAAAAATACCTGGC GATCGCGGATGAGCTGTTTGGTGCGGACTGGGCGGATGCGCGTCACTATCGTTTTGGTGCGAGC**A** **AT**CTGCTGGCGAGCCTGCTGAAGGCGCTGGGTCACGGCGATGGTAAAAGCGCGAGCAGCTACCTC GAGCACCACCACCACCACCAC

DERA-MA$^{S18A/T203A/G239E}$	MTDLKASSLRALKLMDL**A**TLNGDYTDEKVIALCHQAKTPVGNTAAISIYPRSIPIARKTLKEQGT PEIRIATVTNFPHGNDDIDIALAETRAAIAYGADEVDVVFPYRALMAGNEQVGFDLVKACKEACA AANVLLKVIIESGELKDEALIRKASEISIKAGADFIKTSTGLVAVNATPESARIMMEVIRDMGVE KSVGFKV**A**GGARTAEDAQKYLAIADELFGADWADARHYRFGAS**E**LLASLLKALGHGDGKSASSYL EHHHHHH
	ATGACCGACCTGAAGGCGAGCAGCCTGCGTGCGCTGAAACTGATGGATCTG**GCC**ACCCTGAACGG CGACTACACCGATGAGAAGGTTATCGCGCTGTGCCACCAGGCGAAAACCCCGGTGGGTAACACCG CGGCGATCAGCATTTATCCGCGTAGCATCCCGATTGCGCGTAAGACCCTGAAAGAGCAAGGCACC CCGGAAATCCGTATTGCGACCGTTACCAACTTCCCGCACGGTAACGACGATATCGACATTGCGCT GGCGGAAACCCGTGCGGCGATTGCGTACGGCGCGGACGAAGTGGATGTGGTTTTCCCGTATCGTG CGCTGATGGCGGGCAACGAGCAGGTTGGTTTTGATCTGGTGAAGGCGTGCAAAGAAGCGTGCGCG GCGGCGAACGTGCTGCTGAAGGTTATCATTGAGAGCGGTGAACTGAAGGACGAGGCGCTGATCCG TAAAGCGAGCGAAATCAGCATTAAGGCGGGCGCGGATTTCATTAAAACCAGCACCGGTCTGGTGG CGGTTAACGCGACCCCGGAGAGCGCGCGTATCATGATGGAAGTTATTCGTGACATGGGCGTGGAA AAGAGCGTTGGTTTTAAAGTG**GCC**GGTGGCGCGCGTACCGCGGAGGATGCGCAAAAATACCTGGC GATCGCGGATGAGCTGTTTGGTGCGGACTGGGCGGATGCGCGTCACTATCGTTTTGGTGCGAGC**G** **AG**CTGCTGGCGAGCCTGCTGAAGGCGCTGGGTCACGGCGATGGTAAAAGCGCGAGCAGCTACCTC GAGCACCACCACCACCACCAC
DERA-MA$^{S18A/T203A/G239A}$	MTDLKASSLRALKLMDL**A**TLNGDYTDEKVIALCHQAKTPVGNTAAISIYPRSIPIARKTLKEQGT PEIRIATVTNFPHGNDDIDIALAETRAAIAYGADEVDVVFPYRALMAGNEQVGFDLVKACKEACA AANVLLKVIIESGELKDEALIRKASEISIKAGADFIKTSTGLVAVNATPESARIMMEVIRDMGVE KSVGFKV**A**GGARTAEDAQKYLAIADELFGADWADARHYRFGAS**A**LLASLLKALGHGDGKSASSYL EHHHHHH
	ATGACCGACCTGAAGGCGAGCAGCCTGCGTGCGCTGAAACTGATGGATCTG**GCC**ACCCTGAACGG CGACTACACCGATGAGAAGGTTATCGCGCTGTGCCACCAGGCGAAAACCCCGGTGGGTAACACCG CGGCGATCAGCATTTATCCGCGTAGCATCCCGATTGCGCGTAAGACCCTGAAAGAGCAAGGCACC CCGGAAATCCGTATTGCGACCGTTACCAACTTCCCGCACGGTAACGACGATATCGACATTGCGCT GGCGGAAACCCGTGCGGCGATTGCGTACGGCGCGGACGAAGTGGATGTGGTTTTCCCGTATCGTG CGCTGATGGCGGGCAACGAGCAGGTTGGTTTTGATCTGGTGAAGGCGTGCAAAGAAGCGTGCGCG GCGGCGAACGTGCTGCTGAAGGTTATCATTGAGAGCGGTGAACTGAAGGACGAGGCGCTGATCCG TAAAGCGAGCGAAATCAGCATTAAGGCGGGCGCGGATTTCATTAAAACCAGCACCGGTCTGGTGG CGGTTAACGCGACCCCGGAGAGCGCGCGTATCATGATGGAAGTTATTCGTGACATGGGCGTGGAA AAGAGCGTTGGTTTTAAAGTG**GCC**GGTGGCGCGCGTACCGCGGAGGATGCGCAAAAATACCTGGC GATCGCGGATGAGCTGTTTGGTGCGGACTGGGCGGATGCGCGTCACTATCGTTTTGGTGCGAGC**G** **CG**CTGCTGGCGAGCCTGCTGAAGGCGCTGGGTCACGGCGATGGTAAAAGCGCGAGCAGCTACCTC GAGCACCACCACCACCACCAC
DERA-MA$^{S18A/T203A/G239L}$	MTDLKASSLRALKLMDL**A**TLNGDYTDEKVIALCHQAKTPVGNTAAISIYPRSIPIARKTLKEQGT PEIRIATVTNFPHGNDDIDIALAETRAAIAYGADEVDVVFPYRALMAGNEQVGFDLVKACKEACA AANVLLKVIIESGELKDEALIRKASEISIKAGADFIKTSTGLVAVNATPESARIMMEVIRDMGVE KSVGFKV**A**GGARTAEDAQKYLAIADELFGADWADARHYRFGAS**L**LLASLLKALGHGDGKSASSYL EHHHHHH
	ATGACCGACCTGAAGGCGAGCAGCCTGCGTGCGCTGAAACTGATGGATCTG**GCC**ACCCTGAACGG CGACTACACCGATGAGAAGGTTATCGCGCTGTGCCACCAGGCGAAAACCCCGGTGGGTAACACCG CGGCGATCAGCATTTATCCGCGTAGCATCCCGATTGCGCGTAAGACCCTGAAAGAGCAAGGCACC CCGGAAATCCGTATTGCGACCGTTACCAACTTCCCGCACGGTAACGACGATATCGACATTGCGCT GGCGGAAACCCGTGCGGCGATTGCGTACGGCGCGGACGAAGTGGATGTGGTTTTCCCGTATCGTG CGCTGATGGCGGGCAACGAGCAGGTTGGTTTTGATCTGGTGAAGGCGTGCAAAGAAGCGTGCGCG GCGGCGAACGTGCTGCTGAAGGTTATCATTGAGAGCGGTGAACTGAAGGACGAGGCGCTGATCCG TAAAGCGAGCGAAATCAGCATTAAGGCGGGCGCGGATTTCATTAAAACCAGCACCGGTCTGGTGG CGGTTAACGCGACCCCGGAGAGCGCGCGTATCATGATGGAAGTTATTCGTGACATGGGCGTGGAA AAGAGCGTTGGTTTTAAAGTG**GCC**GGTGGCGCGCGTACCGCGGAGGATGCGCAAAAATACCTGGC GATCGCGGATGAGCTGTTTGGTGCGGACTGGGCGGATGCGCGTCACTATCGTTTTGGTGCGAGC**C** **TG**CTGCTGGCGAGCCTGCTGAAGGCGCTGGGTCACGGCGATGGTAAAAGCGCGAGCAGCTACCTC GAGCACCACCACCACCACCAC
DERA-MA$^{S18A/Y49V/T203A}$	MTDLKASSLRALKLMDL**A**TLNGDYTDEKVIALCHQAKTPVGNTAAISI**V**PRSIPIARKTLKEQGT PEIRIATVTNFPHGNDDIDIALAETRAAIAYGADEVDVVFPYRALMAGNEQVGFDLVKACKEACA AANVLLKVIIESGELKDEALIRKASEISIKAGADFIKTSTGLVAVNATPESARIMMEVIRDMGVE KSVGFKV**A**GGARTAEDAQKYLAIADELFGADWADARHYRFGASGLLASLLKALGHGDGKSASSYL EHHHHHH

	ATGACCGACCTGAAGGCGAGCAGCCTGCGTGCGCTGAAACTGATGGATCTG**GCC**ACCCTGAACGG CGACTACACCGATGAGAAGGTTATCGCGCTGTGCCACCAGGCGAAAACCCCGGTGGGTAACACCG CGGCGATCAGCATT**GTG**CCGCGTAGCATCCCGATTGCGCGTAAGACCCTGAAAGAGCAAGGCACC CCGGAAATCCGTATTGCGACCGTTACCAACTTCCCGCACGGTAACGACGATATCGACATTGCGCT GGCGGAAACCCGTGCGGCGATTGCGTACGGCGCGGACGAAGTGGATGTGGTTTTCCCGTATCGTG CGCTGATGGCGGGCAACGAGCAGGTTGGTTTTGATCTGGTGAAGGCGTGCAAAGAAGCGTGCGCG GCGGCGAACGTGCTGCTGAAGGTTATCATTGAGAGCGGTGAACTGAAGGACGAGGCGCTGATCCG TAAAGCGAGCGAAATCAGCATTAAGGCGGGCGCGGATTTCATTAAAACCAGCACCGGTCTGGTGG CGGTTAACGCGACCCCGGAGAGCGCGCGTATCATGATGGAAGTTATTCGTGACATGGGCGTGGAA AAGAGCGTTGGTTTTAAAGTG**GCC**GGTGGCGCGCGTACCGCGGAGGATGCGCAAAAATACCTGGC GATCGCGGATGAGCTGTTTGGTGCGGACTGGGCGGATGCGCGTCACTATCGTTTTGGTGCGAGCG GTCTGCTGGCGAGCCTGCTGAAGGCGCTGGGTCACGGCGATGGTAAAAGCGCGAGCAGCTACCTC GAGCACCACCACCACCACCAC
DERA-MA$^{S18A/Y4 9L/T203A}$	MTDLKASSLRALKLMDL**A**TLNGDYTDEKVIALCHQAKTPVGNTAAISI**L**PRSIPIARKTLKEQGT PEIRIATVTNFPHGNDDIDIALAETRAAIAYGADEVDVVFPYRALMAGNEQVGFDLVKACKEACA AANVLLKVIIESGELKDEALIRKASEISIKAGADFIKTSTGLVAVNATPESARIMMEVIRDMGVE KSVGFKV**A**GGARTAEDAQKYLAIADELFGADWADARHYRFGASGLLASLLKALGHGDGKSASSYL EHHHHHH
	ATGACCGACCTGAAGGCGAGCAGCCTGCGTGCGCTGAAACTGATGGATCTG**GCC**ACCCTGAACGG CGACTACACCGATGAGAAGGTTATCGCGCTGTGCCACCAGGCGAAAACCCCGGTGGGTAACACCG CGGCGATCAGCATT**CTT**CCGCGTAGCATCCCGATTGCGCGTAAGACCCTGAAAGAGCAAGGCACC CCGGAAATCCGTATTGCGACCGTTACCAACTTCCCGCACGGTAACGACGATATCGACATTGCGCT GGCGGAAACCCGTGCGGCGATTGCGTACGGCGCGGACGAAGTGGATGTGGTTTTCCCGTATCGTG CGCTGATGGCGGGCAACGAGCAGGTTGGTTTTGATCTGGTGAAGGCGTGCAAAGAAGCGTGCGCG GCGGCGAACGTGCTGCTGAAGGTTATCATTGAGAGCGGTGAACTGAAGGACGAGGCGCTGATCCG TAAAGCGAGCGAAATCAGCATTAAGGCGGGCGCGGATTTCATTAAAACCAGCACCGGTCTGGTGG CGGTTAACGCGACCCCGGAGAGCGCGCGTATCATGATGGAAGTTATTCGTGACATGGGCGTGGAA AAGAGCGTTGGTTTTAAAGTG**GCC**GGTGGCGCGCGTACCGCGGAGGATGCGCAAAAATACCTGGC GATCGCGGATGAGCTGTTTGGTGCGGACTGGGCGGATGCGCGTCACTATCGTTTTGGTGCGAGCG GTCTGCTGGCGAGCCTGCTGAAGGCGCTGGGTCACGGCGATGGTAAAAGCGCGAGCAGCTACCTC GAGCACCACCACCACCACCAC
DERA-MA$^{S18A/Y4 9F/T203A}$	MTDLKASSLRALKLMDL**A**TLNGDYTDEKVIALCHQAKTPVGNTAAISI**F**PRSIPIARKTLKEQGT PEIRIATVTNFPHGNDDIDIALAETRAAIAYGADEVDVVFPYRALMAGNEQVGFDLVKACKEACA AANVLLKVIIESGELKDEALIRKASEISIKAGADFIKTSTGLVAVNATPESARIMMEVIRDMGVE KSVGFKV**A**GGARTAEDAQKYLAIADELFGADWADARHYRFGASGLLASLLKALGHGDGKSASSYL EHHHHHH
	ATGACCGACCTGAAGGCGAGCAGCCTGCGTGCGCTGAAACTGATGGATCTG**GCC**ACCCTGAACGG CGACTACACCGATGAGAAGGTTATCGCGCTGTGCCACCAGGCGAAAACCCCGGTGGGTAACACCG CGGCGATCAGCATT**TTT**CCGCGTAGCATCCCGATTGCGCGTAAGACCCTGAAAGAGCAAGGCACC CCGGAAATCCGTATTGCGACCGTTACCAACTTCCCGCACGGTAACGACGATATCGACATTGCGCT GGCGGAAACCCGTGCGGCGATTGCGTACGGCGCGGACGAAGTGGATGTGGTTTTCCCGTATCGTG CGCTGATGGCGGGCAACGAGCAGGTTGGTTTTGATCTGGTGAAGGCGTGCAAAGAAGCGTGCGCG GCGGCGAACGTGCTGCTGAAGGTTATCATTGAGAGCGGTGAACTGAAGGACGAGGCGCTGATCCG TAAAGCGAGCGAAATCAGCATTAAGGCGGGCGCGGATTTCATTAAAACCAGCACCGGTCTGGTGG CGGTTAACGCGACCCCGGAGAGCGCGCGTATCATGATGGAAGTTATTCGTGACATGGGCGTGGAA AAGAGCGTTGGTTTTAAAGTG**GCC**GGTGGCGCGCGTACCGCGGAGGATGCGCAAAAATACCTGGC GATCGCGGATGAGCTGTTTGGTGCGGACTGGGCGGATGCGCGTCACTATCGTTTTGGTGCGAGCG GTCTGCTGGCGAGCCTGCTGAAGGCGCTGGGTCACGGCGATGGTAAAAGCGCGAGCAGCTACCTC GAGCACCACCACCACCACCAC
DERA-MA^{S52Y}	MTDLKASSLRALKLMDLSTLNGDYTDEKVIALCHQAKTPVGNTAAISIYPR**Y**IPIARKTLKEQGT PEIRIATVTNFPHGNDDIEIALAETRAAIAYGADEVDVVFPYRALMAGNEQVGFDLVKACKEACA AANVLLKVIIESGELKDEALIRKASEISIKAGADFIKTSTGLVAVNATPESARIMMEVIRDMGVE KSVGFKVTGGARTAEDAQKYLAIADELFGADWADARHYRFGASGLLASLLKALGHGDGKSASSYL EHHHHHH
	ATGACTGATCTGAAAGCAAGCAGCCTGCGTGCACTGAAATTGATGGACCTGTCCACCCTGAATGG CGACTACACCGACGAGAAAGTAATTGCTCTGTGTCATCAGGCCAAAACCCCGGTCGGCAATACCG CCGCTATCAGTATCTATCCTCGC**TAT**ATCCCGATTGCTCGCAAAACACTGAAAGAGCAGGGCACC CCGGAAATCCGTATTGCTACGGTAACCAACTTCCCACACGGTAACGACGACATCGAAATCGCGCT GGCAGAAACCCGTGCGGCAATCGCCTACGGAGCCGATGAAGTTGACGTGGTGTTCCCGTACCGCG

	CGCTGATGGCGGGTAACGAGCAGGTTGGTTTTGACCTGGTGAAAGCTTGTAAAGAGGCCTGCGCG GCAGCGAATGTACTGCTGAAAGTGATCATCGAATCTGGCGAACTGAAAGACGAAGCGCTGATCCG TAAAGCGTCTGAAATCTCCATCAAAGCGGGTGCGGACTTCATCAAAACCTCTACCGGTTTAGTGG CTGTGAACGCGACGCCGGAAAGCGCGCGCATCATGATGGAAGTGATCCGTGATATGGGCGTAGAA AAATCCGTTGGTTTCAAAGTGACGGGCGGCGCGCGTACTGCGGAAGATGCGCAGAAATATCTCGC CATCGCAGATGAGCTGTTCGGTGCTGACTGGGCAGATGCGCGTCACTACCGCTTTGGTGCTTCCG GCCTGCTGGCAAGCCTGTTGAAAGCGCTGGGCCACGGTGATGGTAAGAGCGCCAGCAGCTACCTC GAGCACCACCACCACCACCAC
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DERA-MA$^{S18A/S52F/T203A}$	MTDLKASSLRALKLMDL**A**TLNGDYTDEKVIALCHQAKTPVGNTAAISIYPR**F**IPIARKTLKEQGT PEIRIATVTNFPHGNDDIDIALAETRAAIAYGADEVDVVFPYRALMAGNEQVGFDLVKACKEACA AANVLLKVIIESGELKDEALIRKASEISIKAGADFIKTSTGLVAVNATPESARIMMEVIRDMGVE KSVGFKV**A**GGARTAEDAQKYLAIADELFGADWADARHYRFGASGLLASLLKALGHGDGKSASSYL EHHHHHH
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DERA-MA$^{S18A/S52H/T203A}$	MTDLKASSLRALKLMDL**A**TLNGDYTDEKVIALCHQAKTPVGNTAAISIYPR**H**IPIARKTLKEQGT PEIRIATVTNFPHGNDDIDIALAETRAAIAYGADEVDVVFPYRALMAGNEQVGFDLVKACKEACA AANVLLKVIIESGELKDEALIRKASEISIKAGADFIKTSTGLVAVNATPESARIMMEVIRDMGVE KSVGFKV**A**GGARTAEDAQKYLAIADELFGADWADARHYRFGASGLLASLLKALGHGDGKSASSYL EHHHHHH
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	GATCGCGGATGAGCTGTTTGGTGCGGACTGGGCGGATGCGCGTCACTATCGTTTTGGTGCGAGCG GTCTGCTGGCGAGCCTGCTGAAGGCGCTGGGTCACGGCGATGGTAAAAGCGCGAGCAGCTACCTC GAGCACCACCACCACCACCAC
DERA-MA$^{S142T/A206V}$	MTDLKASSLRALKLMDLSTLNGDYTDEKVIALCHQAKTPVGNTAAISIYPRSIPIARKTLKEQGT PEIRIATVTNFPHGNDDIEIALAETRAAIAYGADEVDVVFPYRALMAGNEQVGFDLVKACKEACA AANVLLKVIIE**T**GELKDEALIRKASEISIKAGADFIKTSTGLVAVNATPESARIMMEVIRDMGVE KSVGFKVTGG**V**RTAEDAQKYLAIADELFGADWADARHYRFGASGLLASLLKALGHGDGKSASSYL EHHHHHH
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DERA-MA$^{S142T/V173A/A206V}$	MTDLKASSLRALKLMDLSTLNGDYTDEKVIALCHQAKTPVGNTAAISIYPRSIPIARKTLKEQGT PEIRIATVTNFPHGNDDIEIALAETRAAIAYGADEVDVVFPYRALMAGNEQVGFDLVKACKEACA AANVLLKVIIE**T**GELKDEALIRKASEISIKAGADFIKTSTGL**A**AVNATPESARIMMEVIRDMGVE KSVGFKVTGG**V**RTAEDAQKYLAIADELFGADWADARHYRFGASGLLASLLKALGHGDGKSASSYL EHHHHHH
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C.2 Site Saturation Mutagenesis

Site Saturation Library Construction and Protein Expression.

The library was constructed using the PCR protocol reported in procedure B of Section C1 and the primers reported in Table S8. The DNA sequence of DERA-MA^{S18A} was used as a template for PCR reaction to create variants of DERA-MA$^{S18A/T203X}$ bearing all 20 amino acids in position 203. Our rationale for this approach was based on the hypothesis that introducing a different amino acid at this position, other than the initially selected alanine, might positively impact the enzyme's reactivity. The workflow for the evolution, involving site-saturation mutagenesis (SSM) at position 203, subsequent selection of the best hits, and individual screening, is illustrated in **Figure S3A**. We also used the DNA sequence of DERA-MA$^{S18A/T203A}$ as a template for SSM at positions A18, L20, I48, Y49, S52, F76, V138, I139, T170, G171, L172, G236, S238, and G239 (**Table S10**). These positions were chosen based on their close proximity (maximum 5 Å distance) to the active site (**Figure S3C**) or because they were identified as a 'hotspot' position by error-prone PCR (i.e., residue S52). Single colonies of the saturation library were picked with sterile toothpicks and used to inoculate 200 µL overnight cultures in a sterile deep-well 96-well 1 mL plate using LB media with 50 µg/mL kanamycin (37 °C, 250 rpm). The following day, 100 µL of the overnight cultures were used to inoculate 1300 µL of LB supplemented with kanamycin. The new plate containing the expression cultures was incubated at 37 °C, with shaking (250 rpm) for 3h. A glycerol stock plate of the library was prepared by mixing sterilized glycerol solution (50% v/v, 100 µL/well) with the remaining overnight cultures (100 µL/well). The glycerol stock library was sealed and stored at -80 °C. After 3h, 100 µL of LB supplemented with 7.5 mM isopropyl β-D-1-thiogalactopyranoside (IPTG) and 50 µg/mL kanamycin was added to the expression cultures, sealed with breath seal and incubated at 25 °C with shaking (250 rpm) overnight. The plate was allowed to grow for 24 hours at 25 °C. After cell growth and expression, cells were harvested by centrifugation (4000 x g, 15 min, 4 °C) and stored at -80 °C before screening.

Table S10. Overview of the three strategies used for directed evolution of DERA MA towards enhanced photodecarboxylase activity.

Starting variant	Evolution strategy	Library size (colonies)	Purified variants	Beneficial Mutations
DERA MA	Error prone PCR	176	3	S52Y
DERA MA	Screening of a previously constructed library of DERA variants [a]	264	9	S142T/A206V, S142T/V173A/A206V
DERA MA$^{S18A/T203A}$	SSM (15 positions, NNK) [b]	1232 (Coverage 94%)	28	Y49V, Y49L, Y49F, S52G, S52F, S52H, G239N, G239E, G239A, G239L

[a] The in-house DERA library was available from the directed evolution campaign of DERA for improved Michael-type addition activity (*30*). [b] Residue positions targeted by site-saturation mutagenesis (SSM) were: A18, L20, I48, Y49, F76, V138, I139, T170, G171, L172, G236, S238, G239, S52, A203. In total, 88 colonies (1 plate) per SSM library were picked for activity screening. In each plate, 2 wells were inoculated with a clean, sterile toothpick (negative control) and 6 wells were inoculated with fresh colonies producing the parental variant for activity reference.

General procedure for screening in 96-well plates (UPLC screening).

The cells were thawed and resuspended in pBER complete bacterial extraction reagent (ThermoFisher, 200 µL/well) and lysed by incubation for 1 h at 25 °C with shaking (250 rpm). The cell lysates were centrifuged (4000 x g, 30 min, 4 °C) and the supernatants (180 µL/well) were transferred into 1 mL clear vials (Analytical Sales and Service Inc.) with stirrer bars (5 mm x 2 mm, VWR) in a 96-well photoredox block (Analytical Sales and Service Inc.). For screening,

10 µL of freshly prepared stock solution of **1a** (50 mM) and 10 µL of (*R*)-**4b** (175 mM) were added in each well. The 96-well block was then sealed, placed on a tumble stirrer (40% rpm, VP 710E-2HM-ICE, V&P Scientific) under a fan and irradiated using a Lumidox II 96-well LED Array (UV405, Analytical Sales and Service Inc.) at stage 2 radiometric power (125 mW) for 24 hours. Then, 200 µL of ethyl acetate containing 1 mM of 4,4'-dimehtylbiphenyl as internal standard was added in each vial, and the plate was sealed, vortexed and centrifuged (4000 × g, 10 min). An aliquot of the supernatants (150 µL) was transferred into 96-well analytical plate containing 150 µL of acetonitrile and subjected for LCMS analysis. LCMS analysis was performed using an Acquity UPLC C18 (1.7µm, 2.1 x 100 mm) column at 35 °C with an isocratic method: 20% of solvent A (10 mM NH_4CO_3 aqueous solution) and 80% of solvent B (95% acetonitrile + 5% of 10 mM NH_4CO_3 aqueous solution) for 3 min at flow rate of 0.4 mL/ min using single ion recording (SIR) to follow the mass of the products. Control experiments (**Figure S3B**) established that the method is suitable for separation of both diastereoisomers with retention times of 1.33 min for *anti*-**5b** and 1.52 min for *syn*-**5b**.

General procedure for screening in 96-well plates (GC-FID screening).
The cells were thawed and resuspended in 100 µL bugbuster (EMD Biosciences, Madison, WI, USA) containing 0.5 µL/mL benzonase and lysed by incubation for 30 min at room temperature under vigorous shaking. The cell lysates were centrifuged (4000 x g, 30 min, 4 °C) and the supernatants (90 µL/well) were transferred into 1 mL clear vials (Analytical Sales and Service Inc.) in a 96-well photoredox block (Analytical Sales and Service Inc.). For screening, 90 µL 50 mM MOPS pH6.5 buffer, 10 µL of freshly prepared stock solution of **1a** (50 mM) and 10 µL of (*R*)-**4a** or (*S*)-**4a** (175 mM) were added in each well. The 96-well block was then sealed and irradiated using a Lumidox II 96-well LED Array (UV405, Analytical Sales and Service Inc.) at stage 3 radiometric power (135 mW) for 24 hours. An aliquot (100 µL) of the reaction mixture was withdrawn and mixed with 100 µL of ethyl acetate containing 2.5 mM of 1,3,5-trimethoxybenzene as internal standard. The resulting solution was vortexed and centrifuged (10000 × g, 3 min). An aliquot of the supernatants (60 µL) was subjected to GC-FID analysis. Control experiments (**Figure S3D**) established that the method is suitable for separation of both diastereoisomers with retention times of 8.80 min for *anti*-**5a** and 8.89 min for *syn*-**5a**.

C.3 Error-prone PCR (epPCR)
The gene coding for *E. coli* DERA MA with a C-terminal His-tag was amplified by error-prone PCR. The PCR reaction (100 µL) was set up with 5 ng of pET26b harbouring the gene coding for DERA MA, 1 U GoTaq MDxHot start polymerase (Promega Corporation, Madison, WI, USA), 0.5 µM of each primer (Fep and Rep, **Table S8**), 1 mM dCTP and dTTP, 0.2 mM dATP and dGTP, 7 mM magnesium chloride, 0.075 mM manganese chloride and GoTaq Flexbuffer. PCR parameters were 95°C, 2 min (initial denaturation), followed by 18 cycles of 95 °C for 30 s, 57 °C (modified according to the Tm of the primers) for 30 s, 72 °C for 1 min, and a final elongation step at 72 °C for 5 min. The resulting linear epPCR fragments and the vector pET26b were digested with *Nde*I and *Xho*I restriction endonuclease (Thermo Fisher Scientific, Waltham, MA, USA), the vector backbone was dephosphorylated, the DNA was purified using a PCR purification kit (Macherey-Nagel, Düren, Germany) and ligated using T4 DNA ligase (Thermo Fisher Scientific, Waltham, MA, USA). The ligation product was purified using a PCR purification kit and used to transform electrocompetent *E. coli* DH5α. Transformants were selected by outgrowth in LB medium, supplemented with 30 µg/ml kanamycin, the plasmid DNA was isolated, and subsequently transformed into *E. coli* BL21(DE3). The library quality was accessed by sequencing the plasmid DNA from several single colonies. Subsequently, single colonies of the error-prone PCR library were picked with sterile toothpicks and used to prepare cell-free extracts for activity screening as described in section C.2.

C.4 Overview of the HTE workflow

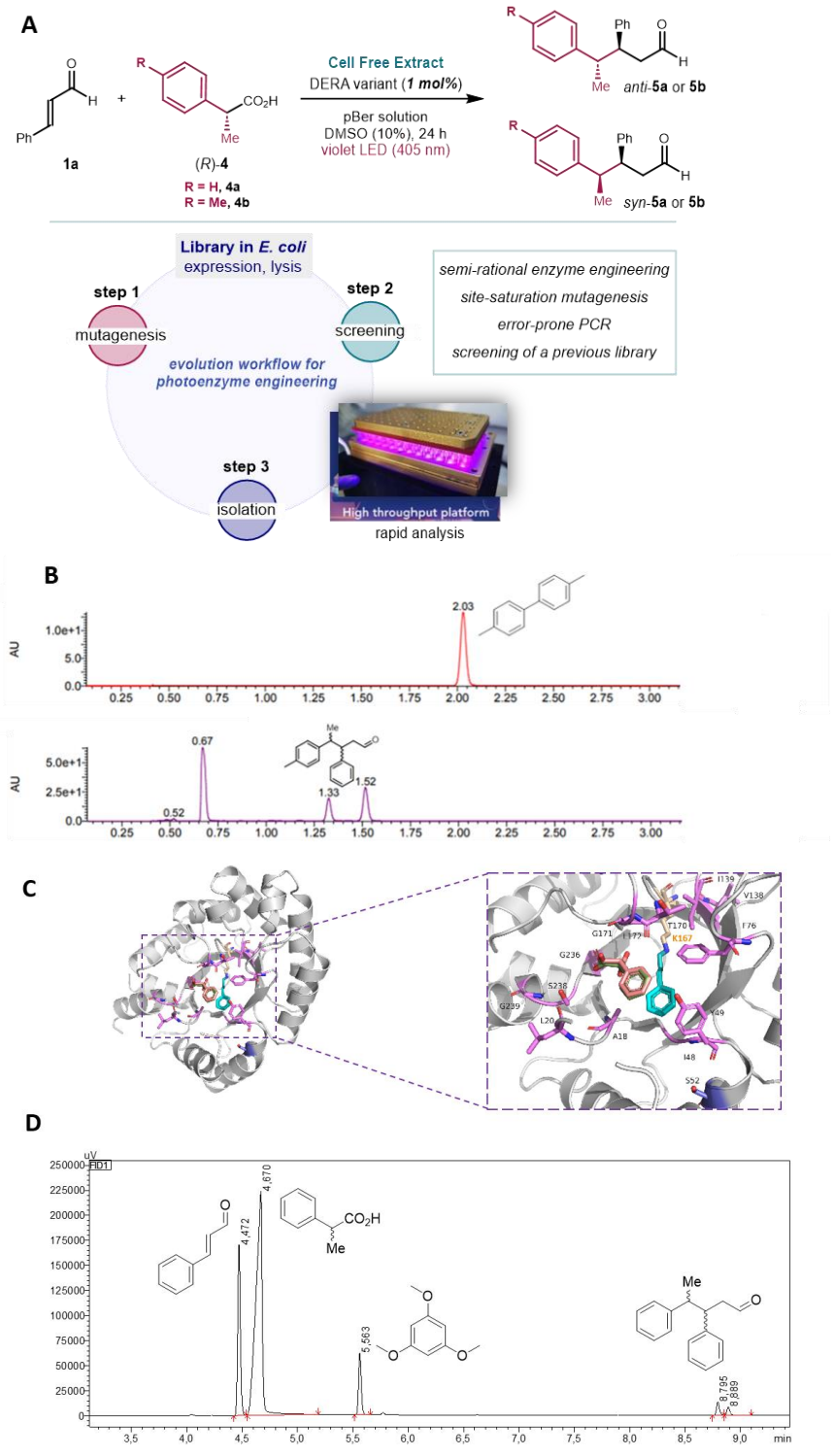


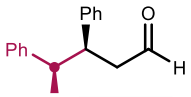
Figure S3. Our implemented HTE workflow for evolution. a) Step 1: construction of site-saturation mutagenesis or error prone PCR libraries; Saturation mutagenesis at position 203 from the DERA-MA^{S18A} template was performed using the reaction of acid (*R*)-**4b** and cinnamaldehyde **1a**, while other studies were conducted using acid (*R*)-**4b**. Step 2: development of a high-throughput screening protocol for reactivity test and analysis of the reactions outcome in 96-well plates; Step 3: isolation of the plasmid and sequencing of gene encoding for the enzyme variant that resulted in the highest conversion to the target product and dr. **b)** Control experiments for the analysis of the photoenzymatic reaction of acid (*R*)-**4b** and **1a** were performed using the parental DERA-MA^{S18A} enzyme, following the same expression and analysis protocols

as used for library screening. **c)** Overlay of the most favorable docked conformations of (*R*)-**4a** (olive) and (*S*)-**4a** (salmon) in the active site of DERA-MA$^{S18A/T203A}$. Cinnamaldehyde **1a** is shown in cyan. The key catalytic residue, lysine 167, is depicted in wheat. Residues in the substrate-binding pocket targeted by site-saturation mutagenesis are shown in magenta. Position S52, identified as a 'hotspot' by error-prone PCR and subsequently targeted for site-saturation mutagenesis, is shown in blue. **d)** Control experiments for the analysis of the photoenzymatic reaction of acid (*R*)-**4a** and **1a** were performed using the parental DERA-MA$^{S18A/T203A}$ enzyme, following the same expression and analysis protocols as used for library screening.

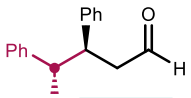
Summary of the Directed Evolution Campaign (Table S11). Using the original best mutant DERA-MA$^{S18A/T203A}$ as a template, we performed site-saturation mutagenesis (SSM) at 15 amino acid positions (A18, L20, I48, Y49, S52, F76, V138, I139, T170, G171, L172, G236, S238, G239, A203). These positions were selected based on their proximity (maximum 5 Å distance) to the active site, as indicated by the docking model of DERA-MA$^{S18A/T203A}$. SSM at these positions revealed two '*hotspot*' residues, Y49 and particularly ***G239***, where several single mutations led to improved activity (Table S11, entries 2-8). For the least reactive substrate (*S*)-**4a**, the best variant, DERA-MA$^{S18A/T203A/G239A}$ (entry 4), showed a threefold increase in turnover number (TON = 18) and substantially enhanced diastereoselectivity (21.5:1 dr) compared to the parental enzyme DERA-MA$^{S18A/T203A}$ (TON = 6). This variant also demonstrated higher activity with carboxylic acid (*R*)-**4a** (TON = 17 vs. 10), while maintaining similar stereochemical outcomes as the parental enzyme.

Table S11: Summary of the Directed Evolution Campaign.

directed evolution campaign



syn-**5a** (99% ee)



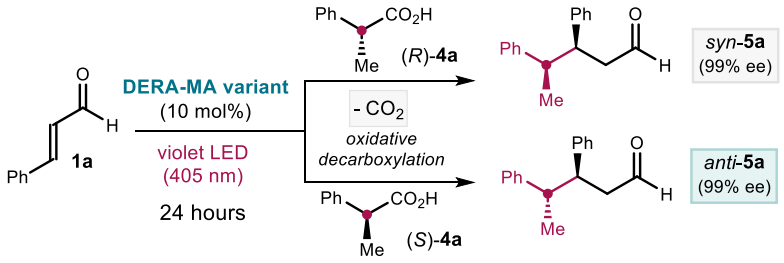
anti-**5a** (99% ee)

entry	mutation	from (*R*)-**4a** (*TON*)	from (*S*)-**4a** (*TON*)	
1	**S18A + T203A**	10%, 7.1:1 dr (*10*)	6%, 9.5:1 dr (*6*)	*site-saturation mutagenesis*
2	**S18A + T203A + G239N**	18%, 8.6:1 dr (*18*)	10%, 13.4:1 dr (*10*)	
3	**S18A + T203A + G239E**	19%, 8:1 dr (*19*)	10%, 12.8:1 dr (*10*)	
4	**S18A + T203A + G239A**	17%, 9.8:1 dr (*17*)	18%, 21.5:1 dr (*18*)	
5	**S18A + T203A + G239L**	16%, 10.2:1 dr (*16*)	13%, 19.1:1 dr (*13*)	
6	**S18A + Y49V + T203A**	11%, 8.9:1 dr (*11*)	6%, 9.1:1 dr (*6*)	
7	**S18A + Y49L + T203A**	13%, 8.3:1 dr (*13*)	6%, 7.2:1 dr (*6*)	
8	**S18A + Y49F + T203A**	14%, 7.8:1 dr (*14*)	7%, 6.4:1 dr (*7*)	
9	**S52Y**	21%, 1.3:1 dr (*21*)	5%, 1.9:1 dr (*5*)	*error-prone PCR*
10	**S18A + S52G + T203A**	18%, 10:1 dr (*18*)	7%, 13.2:1 dr (*7*)	
11	**S18A + S52F + T203A**	11%, 7.2:1 dr (*11*)	9%, 11.9:1 dr (*9*)	
12	**S18A + S52H + T203A**	11%, 6.8:1 dr (*11*)	10%, 11.1:1 dr (*10*)	
13	**S142T + A206V**	18%, 1.7:1 dr (*18*)	6%, 1.8.1 dr (*6*)	*screening of a previous library*
14	**S142T + V173A + A206V**	22%, 1.8:1 dr (*22*)	7%, 1.9:1 dr (*7*)	

Reactions performed using DERA-MA variants (1 mol%) on a 1.25 µmol scale of **1a** (c = 2.5 mM) in MOPS buffer (50 mM) at pH 6.5 in 10% of DMSO. Conversion to products **5** are the average of two runs. TON, turnover number.

In a different engineering approach, we subjected DERA-MA to random mutagenesis via error-prone PCR, identifying residue S52 as an additional 'hotspot' (entry 9). We then performed site-saturation mutagenesis (SSM) at position S52 using DERA-MA$^{S18A/T203A}$ (our best original enzyme) as the template. This led to the identification of DERA-MA$^{S18A/S52G/T203A}$ as the best variant (entry 10), which exhibited significantly enhanced activity and diastereoselectivity.
Finally, we screened a previously constructed library of DERA mutants (*30*) and identified additional mutations that give improved activity (entries 13-14). The best variant, DERA-MA$^{S142T/V173A/A206V}$ (entry 14) displayed a significantly enhanced activity over DERA-MA$^{S18A/T203A}$ when using (*R*)-**4a**, showing the highest turnover number (**TON = 22**).

This evolution campaign, based on three different approaches, led to the identification of three top mutants: site-saturation mutagenesis, leading to DERA-MA$^{S18A/T203A/G239A}$; error-prone mutagenesis, identifying DERA-MA$^{S18A/S52G/T203A}$; and screening a previous library of DERA enzymes, which led us to identify DERA-MA$^{S142T/V173A/A206V}$ with improved turnover. We tested the activity of the three best identified variants under the same conditions used to assess the generality of the reactions. Specifically, we used these three enzymes at 10 mol% to directly compare their performance with that of our previous best mutant, DERA-MA$^{S18A/T203A}$. The performance of these enzymes and their comparison are detailed in Scheme S1 below. Despite demonstrating better turnover numbers at 1 mol%, these variants performed similarly to or worse than DERA-MA$^{S18A/T203A}$ under the optimized reaction conditions. This is likely due to a reduced stability of the new enzymes under these conditions.



entry	mutation	from (*R*)-**4a**	from (*S*)-**4a**
1	**DERA-MA$^{S18A/T203A}$**	66%, 6.6:1 dr	34%, 11.5:1 dr
2	**DERA-MA$^{S18A/T203A/G239A}$**	48%, 5:1 dr	34%, 29:1 dr
3	**DERA-MA$^{S18A/S52G/T203A}$**	**73%**, 8.6:1 dr	39%, 15:1 dr
4	**DERA-MA$^{S142T/V173A/A206V}$**	21%, 1.6:1 dr	27%, 2.2:1 dr

Scheme S1. Comparison of the evolved mutants under the reaction conditions. Reactions performed with 10 mol% of enzymes (125 µM) on a 0.63 µmol scale of **1a** (1.25 mM) in 50 mM MOPS buffer at pH 6.5 in 10% of DMSO for 24 hours.

D. Enzyme Expression and Purification

For heterologous expression of all enzymes, *E. coli* BL21(DE3) (New England BioLabs, NEB) was used as host organism. All enzymes were cloned in pET26b vector with a C-terminus His-Tag and without the pelB signal peptide. Transformations were performed at 42 ˚C for 10 seconds according to the standard protocol (NEB).

For expression of all enzymes, the following protocol was used: 400 mL of LB medium, supplemented with kanamycin (50 µg mL^{-1}) were inoculated with 7 mL of pre-culture. The cells were allowed to grow at 37 °C until an OD_{600} of 0.7-1 was reached. Expression of the enzymes were performed by inducing the main cultures with 0.5 mM of isopropyl β-D-1-thiogalactopyranoside (IPTG) and cultures were grown overnight at 25 °C with shaking at 170 rpm. The next day, the cells were harvested by centrifugation (4.700 g, 20 min, 4 °C), resuspended in lysis buffer (50 mM KH_2PO_4, 300 mM NaCl, 10 mM imidazole, pH 8.0), and lysed by ultrasonication.

Protein purification was performed by Ni-NTA affinity chromatography using pre-packed Ni-NTA HisTrap FF columns (GE Healthcare) according to the manufacturer´s instructions. After sonication, the enzyme solution was filtrated with a 0.45 µm filter and loaded into the column, which has been previously equilibrated with lysis buffer. After loading of the filtered lysate, the column was washed with sufficient amounts of lysis buffer (50 mL) and washing buffer (50 mM KH_2PO_4, 300 mM NaCl, 25 mM imidazole, pH 8.0, 25 mL). The bound protein was recovered with elution buffer (50 mM KH_2PO_4, 300 mM NaCl, 300 mM imidazole, pH 8.0). The process of purification was monitored with SDS-PAGE and fractions containing pure protein were pooled. Pooled fractions were used for buffer exchange using PD-10 columns (Cytiva) and enzymes were obtained in potassium phosphate (KPi) or 3-(*N*-Morpholino)-Propanesulfonic Acid (MOPS) buffer (50 mM, pH 6.5). Protein concentration was determined spectrophotometrically using the extinction coefficient at 280 nm. Typically, a protein yield of 30-50 mg per gram of cell culture was obtained. The purity of the enzymes was examined by SDS-PAGE analysis (**Figure S4**).

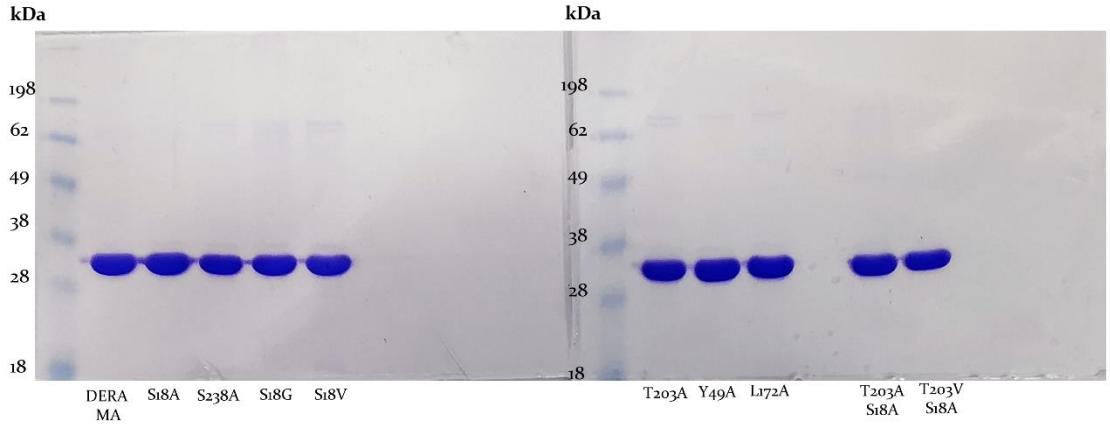


Figure S4. SDS-PAGE analysis for purity of the enzymes used in this study. In total 7 µg of each enzyme was loaded into the SDS-PAGE. From left to right: DERA-MA (MW = 28629.7), $DERA^{S18A}$ (MW = 28613.7), $DERA^{S238A}$ (MW = 28613.7), $DERA^{S18G}$ (MW = 28599.7), $DERA^{S18V}$ (MW = 28641.7), $DERA^{T203A}$ (MW = 28599.7), $DERA^{Y49A}$ (MW = 28537.6), $DERA^{L172A}$ (MW = 28587.6), $DERA^{S18A/T203A}$ (MW = 28583.7), $DERA^{S18A/T203V}$ (MW = 28611.7).

E. Computational Studies

The molecular dockings were performed using Autodock Vina as tool incorporated into YASARA. The crystal structure of DERA-MA forming the iminium ion intermediate was used as receptor (PDB: 7P76). In instances where variants of DERA-MA were used, all mutations to the parental enzyme were simulated in silico using the YASARA structure software with the AMBER 03 force field (35). After the introduction of a mutation or modification, the energy of the system was minimized following a three-step protocol deformation. In step one, only the atoms constituting the mutated amino acid residue were subjected to energy minimization. In step two, the process for energy minimization was repeated by including all the atoms of the amino acid residues that are located within 6 Å distance from the mutated residue. In step three, the energy of the overall structure was minimized.

In all dockings (**Table S12**), the simulation box was placed 10 Å around the active site of the enzyme.

Table S12. Dockings performed in this study.

Entry	**Enzyme**	**Substrate**	Docking clusters	*Binding energy (Kcal/mol)*
1	DERA-MA	**2a**	**001**	**000006.0750**
			002	000004.7720
			003	000003.8890
			004	000003.1530
			005	000003.0230
2	DERA-MA^{S18A}	**2a**	**001**	**000005.9100**
			002	000004.5360
			003	-00001.6200
			004	-00021.6400
			005	-00150.4800
3	DERA-MA^{S18A}	(*R*)-**4a**	**001**	**000006.0630**
			002	000004.6130
			003	000001.3530
			004	-00072.6160
4	DERA-MA$^{S18A/T203A}$	(*S*)-**4a**	**001**	**000006.1970**
			002	**000005.0210**
			003	000004.4900
			004	000003.7000
			005	000002.7110
			006	000002.0480
5	DERA-MA$^{S18A/T203A}$	(*R*)-**4a**	001	**000006.2160**
			002	000004.7170
			003	000004.4560
			004	000003.5500
6	DERA-MA$^{S18A/S238A}$	**2a**	**001**	**000005.2040**
			002	**000005.0220**
			003	000003.8290
			004	-00022.0720

For each simulation, 25 VINA docking runs of each ligand to the receptor were run. Results were sorted by binding energy. More positive energies indicate stronger binding and negative energies mean no binding. All binding poses were inspected visually.
In each case, the docking outcomes guided us to choose the best binding energy as the most compelling option. For example, **Figure S5** shows that in most cases the second-best binding pose obtained (**Table S12**, entries 1-3 and 5, referred to as **002** in Figure 1, substrate in green) are very unlikely to represent a productive binding pose. This is because the substrate binds in a cavity distant from the active site, where the reactive iminium ion is accommodated. We believe that these binding poses are highly unlikely to provide a productive scenario or have any influence on the yield and selectivity of the reactions, because the carboxylic acid substrate, being far away from the active site, could not effectively react with the iminium ion.

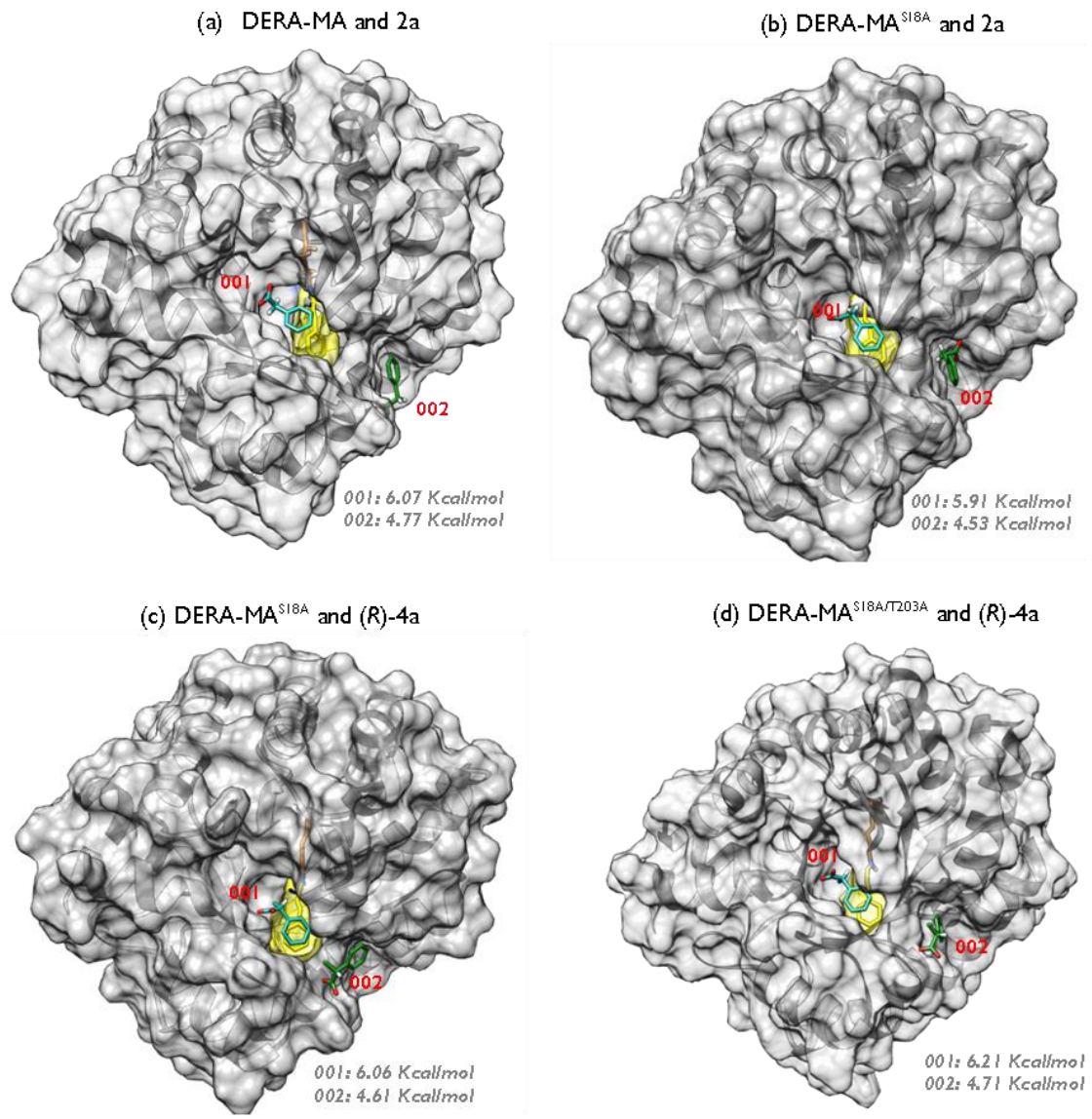


Figure S5. Binding poses with the highest binding energies for carboxylic acid **2a** (turquoise or green) into the active site of: (**a**) DERA-MA, (**b**) DERA-MA$^{S18A/T203A}$ and for (*R*)-**4a** into the active site of (**c**) DERA-MA^{S18A} and (**d**) DERA-MA$^{S18A/T203A}$. The iminium ion formed upon condensation of **1a** with K167 is shown in yellow. In all cases the substrate with the highest binding energy (**pose 001**) is shown in turquoise while the one with second-best binding pose (**pose 002**) is shown in green.

Only in one case, when using DERA-MA$^{S18A/T203A}$ with substrate (*S*)-**4a**, we obtained two distinct and meaningful binding poses (entry 4 in **Table S12**). These two outcomes are visually represented in **Figure S6** below for clarity. In the first binding pose (**Figure S6A**), with a binding energy of 6.1970 kcal/mol, the methyl group of the α-stereogenic carbon in (*S*)-**4a** is oriented towards the newly introduced A203 residue. Conversely, the second-best binding pose, characterized by a binding energy of 5.0210 kcal/mol, exposes the same methyl group to the aqueous environment outside the enzyme's active site (**Figure S6B**). This alternative binding pose would result in the opposite enantiomer of the reaction product. Specifically, decarboxylation of (*S*)-**4a** in this pose, followed by radical coupling, would theoretically retain the stereocenter in the product (C-C bond formation would not require inversion of configuration, since the two radicals would face each other). However, this outcome does not align with experimental observations, as inversion of configuration at the enantiopure carboxylic acid was observed.
Furthermore, if this scenario were accurate, introducing the bulky valine at position 203 would not be expected to significantly impact the enzyme's reactivity with (*S*)-**4a** as a substrate. Yet, experimental results with DERA-MA$^{S18A/T203V}$ demonstrated a substantial reduction in reactivity (9% yield) compared to the DERA-MA$^{S18A/T203A}$ variant (47% yield) when using (*S*)-**4a** as the substrate.
On the basis of this reasoning, the binding pose with the highest energy (**Figure S6A**) has been considered the most relevant one for this study.

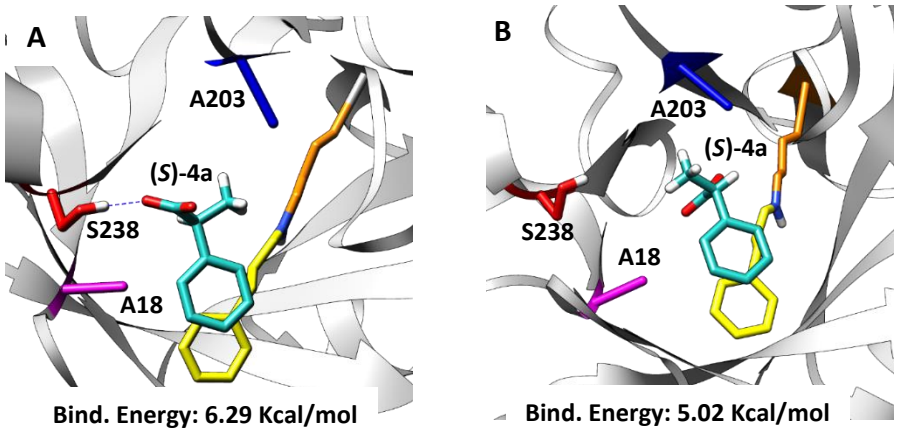


Figure S6. Molecular dockings of (*S*)-**4a** (turquoise) into the active site of DERA-MA$^{S18A/T203A}$. The iminium ion formed upon condensation of **1a** with the catalytic K167 is shown in yellow. Mutation S18A and T230A are shown in magenta and blue, respectively. All dockings were performed with YASARA structure. UCSF Chimera 1.11 was used for visualization.

To better evaluate the effect of S238 on the stabilization of substrate **2a** in the active site of DERA-MA^{S18A}, we introduced the S238A mutation in silico, following the protocol outlined in section E of the Supporting Information. Docking **2a** into the new variant DERA-MA$^{S18A/S238A}$ (see Table S12, entry 6) resulted in two meaningful binding poses with binding energies of 5.20 Kcal/mol (**Figure S7A**) and 5.02 Kcal/mol (**Figure S7B**). In both cases, the binding energy is significantly lower than that observed for the same substrate using the DERA-MA^{S18A} single variant (5.91 Kcal/mol, **Figure S7C**). The results indicate that, in the absence of S238, the carboxylate of **2a** forms hydrogen bonding interactions with Y49 (**Figure S7A**) or T19 (**Figure S7B**) in the active site. In both cases, the distance between the reactive carbon of **2a** and the β-carbon of the iminium ion is around 5.5 Å, considerably longer than the distance observed for the variant with a serine at position 238 (3.7 Å, **Figure S7C**). Therefore, considering: i) the poor binding energies in all dockings with the enzyme containing the S238A mutation, ii) the increased distance between the reactive carbons, and iii) the very poor reactivity of the DERA-MA^{S238A} variant with **2a** (result in the main paper, Figure 2a, 7% yield in the model reaction), we conclude that S238 plays an essential role in securing the substrate in a productive binding pose.

Additionally, we generated the DERA-MA$^{S18A/S238A}$ mutant used in these computational studies and tested it in the laboratory with substrate **2a**. The results revealed that product **3a** was obtained in a 29% yield, significantly lower than the yield obtained with the variant bearing serine at position 238 (DERA-MA^{S18A}, which afforded product **3a** in 57% yield, results in Figure 2a of the main paper). This experimental outcome aligns with the findings from the docking studies using the same variant, further confirming that the hydrogen bonding enabled by S238 brings the carboxylic acid in closer proximity to the iminium ion, underscoring its positive role in catalysis.

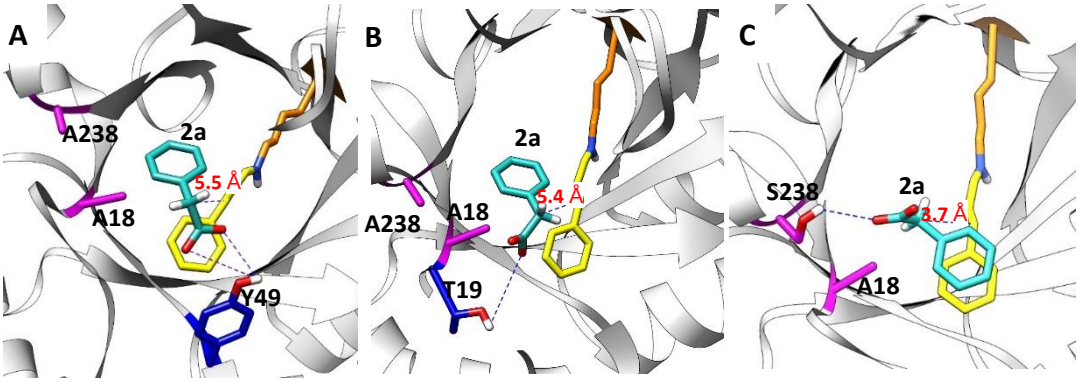
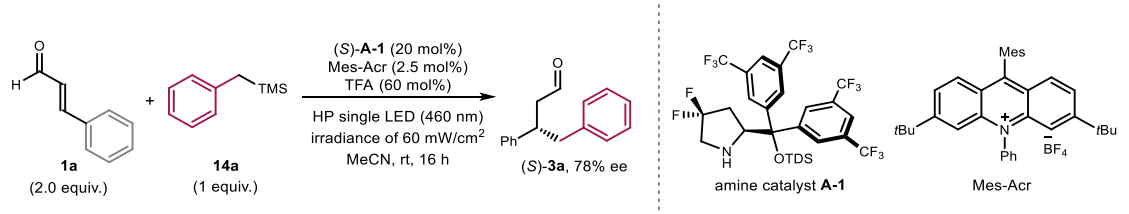


Figure S7. (A, B) Binding poses identified by molecular docking of **2a** (turquoise) into the active site of DERA-MA$^{S18A/S238A}$ and (C) binding pose of **2a** into the active site of DERA-MA^{S18A}. In all dockings the iminium ion formed upon condensation of **1a** with the catalytic K167 is shown in yellow. All dockings were performed with YASARA structure. UCSF Chimera 1.11 was used for visualization.

F. Determination of the Stereochemistry of the Products

F.1 Determination of the Absolute Configuration of Product 3a



The absolute configuration of product **3a** was inferred by comparison with literature data (*34*). Specifically, we replicated the procedure described in the literature using the chiral small organocatalyst **A-1** and compared the optical rotation and UPC2 spectra of **3a** with the product obtained through the photoenzymatic reaction (**Figure S8**). According to the literature procedure, product (*S*)-**3a** was obtained with an enantiomeric excess of 78%. In contrast, the photoenzymatic reaction yielded the opposite enantiomer with 99% ee. Therefore, the enzymatic product was determined to be (*R*)-**3a**.

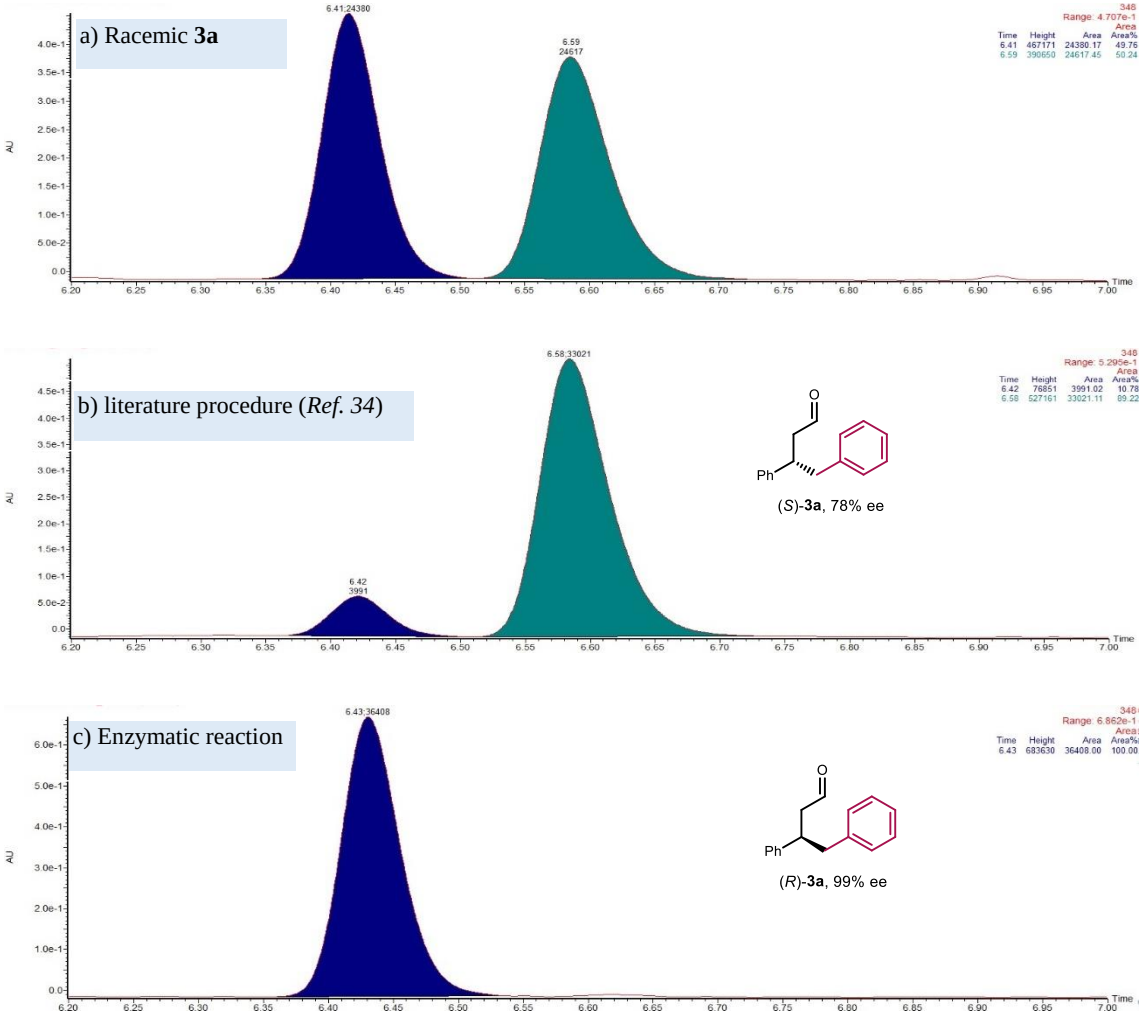
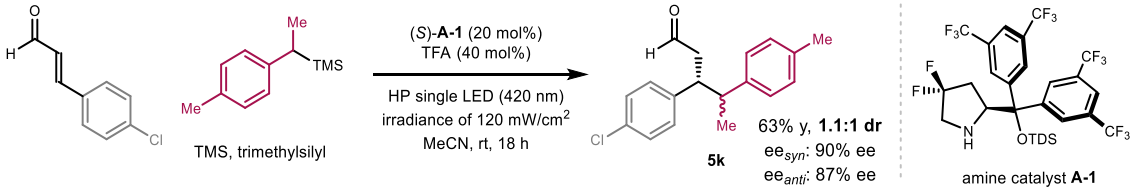


Figure S8: UPC^2 traces of **3a** synthesized a) as a racemic mixture, b) using a literature procedure (*34*), and c) using our photobiocatalytic protocol with DERA-MA^{S18A}.

F.2 Determination of the Absolute and Relative Configuration of Products 5

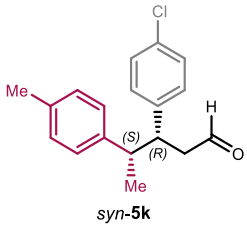
The relative and absolute configuration of product **5k** was inferred by comparison with a reference compound synthesized using a chiral small molecule organocatalyst and crystallized as a single stereoisomer suitable for X-ray crystallographic analysis. The procedure for the synthesis of the reference compound was adapted from the literature (*24*), and is detailed below.

Synthesis of reference compound 3-(4-Chlorophenyl)-4-(*p*-tolyl)pentanal 5k



A dry vial was charged with *p*-chloro-cinnamaldehyde **1e** (1.5 equiv., 0.6 mmol, 144.0 mg), trimethyl(1-(p-tolyl)ethyl)silane (1 equiv., 0.4 mmol, 77.0 mg) and the chiral amino catalyst (*S*)-**A-1** (10 mol%, 0.04 mmol, 28.2 mg). The vial was sealed with a septum, flushed with argon and CH_3CN (0.4 mL) and TFA (20 mol%, 0.08 mmol, 6.1 µL) was added. The heterogeneous mixture was stirred for 18 h under irradiation at 420 nm (single LED, 120 mW/cm^3) at ambient temperature. The mixture was purified by two consecutive column chromatography steps (silica gel, step 1. 20% dichloromethane in hexanes, step 2. 5% EtOAc in hexanes) afforded the desired product **5k** in 63% yield (72.8 mg) as a 1:1.1 mixture of diastereomers.

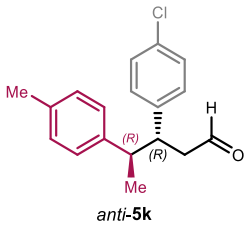
This result indicates that small-molecule organocatalysis cannot provide control of the relative configuration, highlighting the unique ability of our photoenzymes to achieve this challenging target. Preparative TLC (thin layer chromatography, silica gel, 15% EtOAc in hexanes) enabled separation and isolation of the individual *syn* and *anti* diastereoisomers of products **5k**. Crystals from compound *syn*-**5k** were suitable for X-ray analysis, which secured the absolute and relative configuration of the product (see *Section K* for details, CCDC 2280852).



***syn-(3R,4S)*-3-(4-Chlorophenyl)-4-(p-tolyl)pentanal** was obtained in 28.1 mg (24%) as a single diastereomer – the <u>*absolute and relative configuration was unambiguously determined by x-ray crystallographic analysis*</u> (see *section K*). The enantiomeric excess was determined to be 90% *via* analysis of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine), which could be separated by UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 70:30 CO_2/*i*PrOH for 5 min; isocratic 70:30 CO_2/*i*PrOH for 9 min, gradient from 70:30 CO_2/*i*PrOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 347 nm, *syn*-**5k**: τ_{minor} = 10.8 min and τ_{major} = 11.0 min.

<u>^{1}H NMR</u> (500 MHz, $CDCl_3$): δ 9.36 (dd, *J* = 2.3, 1.3 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.1 Hz, 2H), 3.27 (td, *J* = 10.1, 4.6 Hz, 1H), 2.86 – 2.78 (m, 1H), 2.59 (ddd, *J* = 17.0, 9.9, 2.4 Hz, 1H), 2.50 (ddd, *J* = 17.0, 4.6, 1.4 Hz, 1H), 2.34 (s, 3H), 1.02 (d, *J* = 6.9 Hz, 3H). <u>^{13}C NMR</u> (126 MHz, $CDCl_3$): δ 201.23, 141.81, 141.49, 136.54, 132.57, 129.60, 129.57, 128.90, 127.54, 49.09, 46.92, 45.55, 21.17, 20.60.

<u>HRMS (APCI):</u> calculated for calculated for $C_{18}H_{18}ClO$: 285.1041; found: 285.1036.



anti-**5k**

anti-(3R,4R)-3-(4-Chlorophenyl)-4-(p-tolyl)pentanal was obtained in 22 % yield (25.3 mg) as a single diastereomer. Enantiomeric excess was determined to be 87% *via* analysis of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine), which could be separated by UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 70:30 CO_2/*i*PrOH for 5 min; isocratic 70:30 CO_2/*i*PrOH for 9 min, gradient from 70:30 CO_2/*i*PrOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 347 nm, ***anti*-5k**: τ_{minor} = 11.3 min and τ_{major} = 11.8 min.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.58 (dd, *J* = 2.3, 1.6 Hz, 1H), 7.15 (d, *J* = 8.6 Hz, 2H), 7.01 (d, *J* = 7.8 Hz, 2H), 6.90 (d, *J* = 8.3 Hz, 2H), 6.85 (d, *J* = 7.9 Hz, 2H), 3.47 – 3.39 (m, 1H), 3.00 (p, *J* = 7.0 Hz, 1H), 2.81 (ddd, *J* = 16.9, 5.7, 1.6 Hz, 1H), 2.74 (ddd, *J* = 16.9, 9.3, 2.3 Hz, 1H), 2.28 (s, 3H), 1.25 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.62, 140.36, 140.23, 136.10, 132.36, 130.03, 128.93, 128.33, 128.04, 46.56, 45.93, 44.53, 21.11, 18.48.

Racemic samples of adduct **5k** were prepared using the organocatalytic procedure described above on a 0.1 mmol scale using the racemic amine catalyst **A-1**. The racemic product **5k** was isolated in 55% yield (16.8 mg) as a 1:1.3 mixture of diastereoisomers. Separation of diastereoisomers by preparative TLC afforded racemic, diastereomerically pure samples of *syn* and *anti* **5k** (**Figures S9 and S10**).

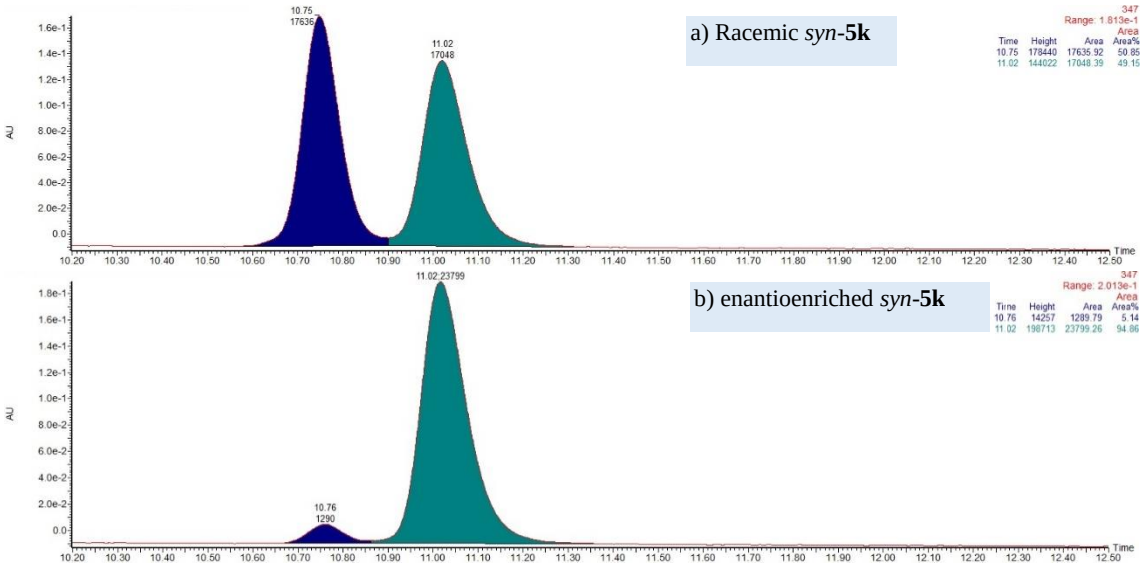


Figure S9. UPC^2 analysis of racemic (top) and enantioenriched (bottom) *syn*-**5k**, prepared via the organocatalytic route with catalyst **A-1**

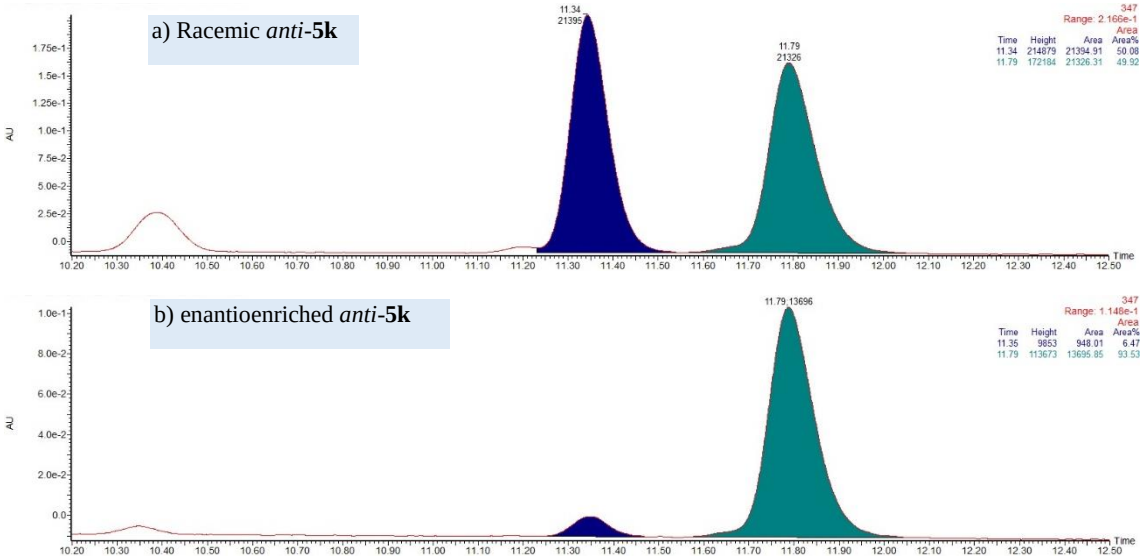
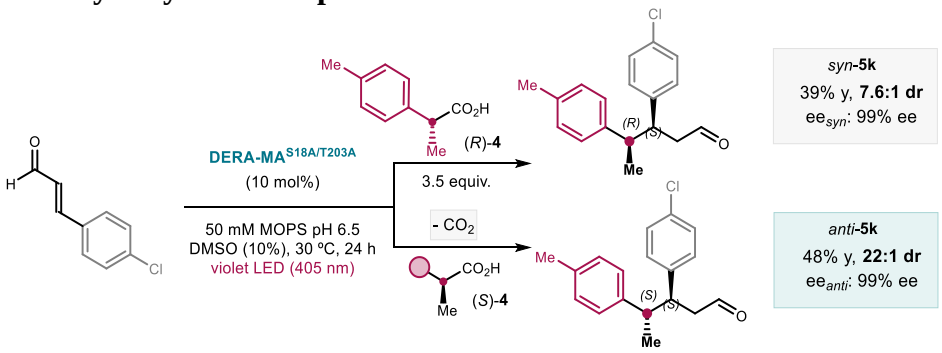


Figure S10. UPC^2 analysis of racemic (top) and enantioenriched (bottom) *anti*-**5k**, prepared via the organocatalytic route with catalyst **A-1**

Photobiocatalytic synthesis of product 5k



Determination of the relative configuration of the enzymatic product 5k by GC-FID

The isolated diastereomers *syn*-**5k** and *anti*-**5k**, prepared via the organocatalytic route with catalyst **A-1** mentioned above, were analyzed by GC-FID analysis, which allowed assignment of the individual retention times of both diastereoisomers (**Figure S11**).

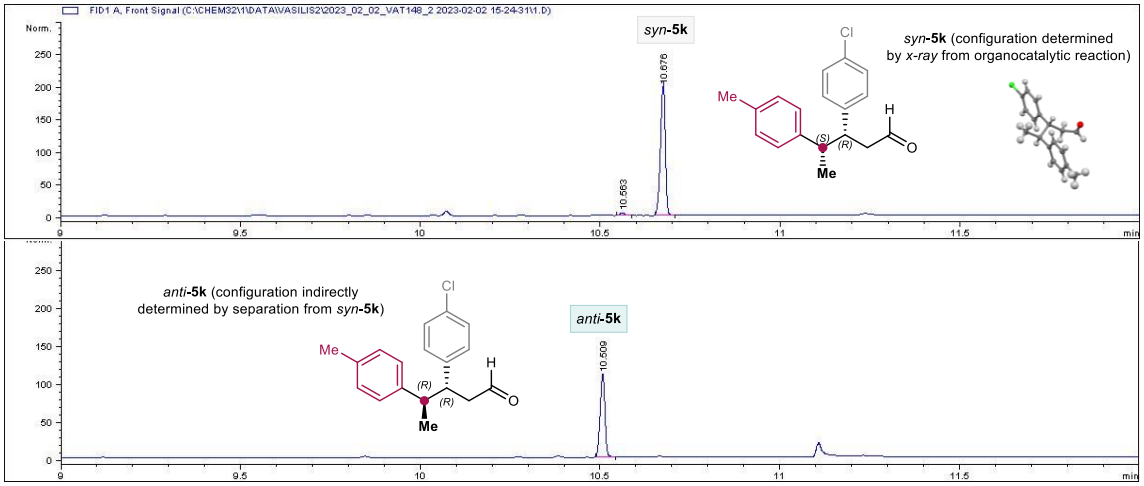


Figure S11. GC-FID analysis of *syn*-**5k** (top) and *anti*-**5k** (bottom), prepared via the organocatalytic route with catalyst **A-1**

These references served to establish the relative configuration of the biocatalytic products **5k**. GC-FID analysis the enzymatic reaction catalyzed by DERA-MA^{S18A} and starting from *(R)*-**4b** showed a retention time consistent with the *syn*-**5k** diastereomer, confirming its identity (shown at the top of **Figure S12**). Conversely, GC-FID analysis of the product of the enzymatic reaction catalyzed by DERA-MA^{S18A} and starting from *(S)*-**4b** matched the retention time of *anti*-**5k** (bottom in **Figure S12**).

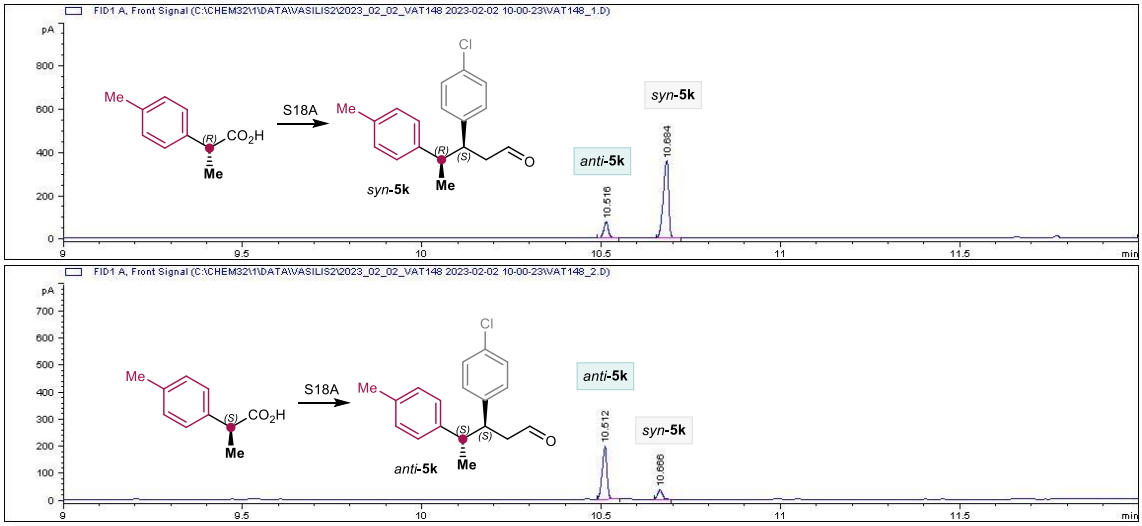


Figure S12. GC-FID analysis of the enzymatic reaction catalyzed by DERA^{S18A} using (*R*)-**4k** (top) or (*S*)-**4k** (bottom), affording *syn*-**5k** or *anti*-**5k** respectively.

Determination of the absolute configuration of 5k by UPC^2 analysis

The absolute configuration of adducts **5k** prepared via the photoenzymatic reaction was established by UPC^2 analysis and comparison with the reference samples prepared via the organocatalytic route. This comparison further confirmed the relative configuration of the enzymatic products. Specifically, we used the isolated enantioenriched and racemic products of *syn*-**5k** and *anti*-**5k**, prepared via the organocatalytic route with catalyst **A-1**, to assign the individual retention times of all 4 possible stereoisomers.

UPC^2 analysis of the products of the enzymatic reaction catalyzed by DERA-MA^{S18A} using *(R)*-**4b** confirmed that *syn*-**5k** was preferentially formed (**Figure S13**). Conversely, analysis of the product of the enzymatic reaction catalyzed by DERA-MA^{S18A} and starting from *(S)*-**4b** showed a retention time consistent with the *anti*-**5k** diastereomer.

This analysis also allowed us to unambiguously assign the absolute configuration of the enzymatic products **5k**. X-ray analysis of *syn*-**5k**, prepared via the organocatalytic route using catalyst (*S*)-**A-1**, established an (3*R*,4*S*) absolute configuration. Direct comparison of the UPC traces of *syn*-**5k**, prepared via the enzymatic route, showed that the opposite enantiomer was formed instead, establishing an (3*S*,4*R*) absolute configuration.

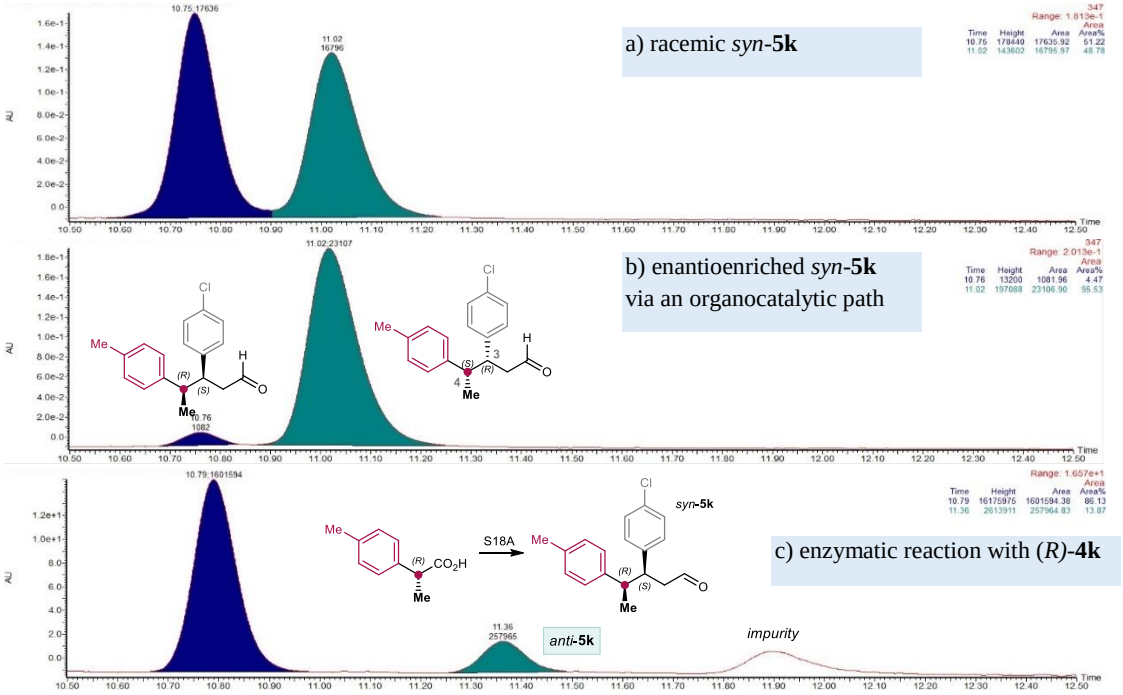


Figure S13. UPC analysis of (**a**) racemic *syn*-**5k**, (**b**) enantioenriched *syn*-**5k** prepared via the organocatalytic route with catalyst **A-1**, (**c**) *syn*-**5k** prepared via the enzymatic reactions performed with DERA^{S18A} using (*R*)-**4k**.

We then repeated the same comparison to establish the stereochemistry of the *anti*-**5k** prepared via the enzymatic reaction catalyzed by DERA-MA^{S18A}. First, we confirmed that using the chiral carboxylic acid *(S)*-**4b** the *anti*-**5k** was preferentially formed (**Figure S14**).

The absolute configuration of X-ray analysis of *anti*-**5k**, prepared via the organocatalytic route using catalyst (*S*)-**A-1**, was established to be (3*R*,4*R*). This conclusion is based on the fact that the chiral amine catalyst **A1** has the ability to control only the formation of the stereogenic center at the 3 position. Consequently, the absolute configuration of this stereogenic center remained unchanged in comparison to the *syn*-**5k** adduct (for which we obtained unambiguous evidence of the absolute configuration through X-ray analysis). Direct comparison of the UPC traces of *anti*-**5k**, prepared via the enzymatic route from *(S)*-**4b**, showed that the opposite enantiomer was formed instead, establishing an (3*S*,4*S*) absolute configuration.

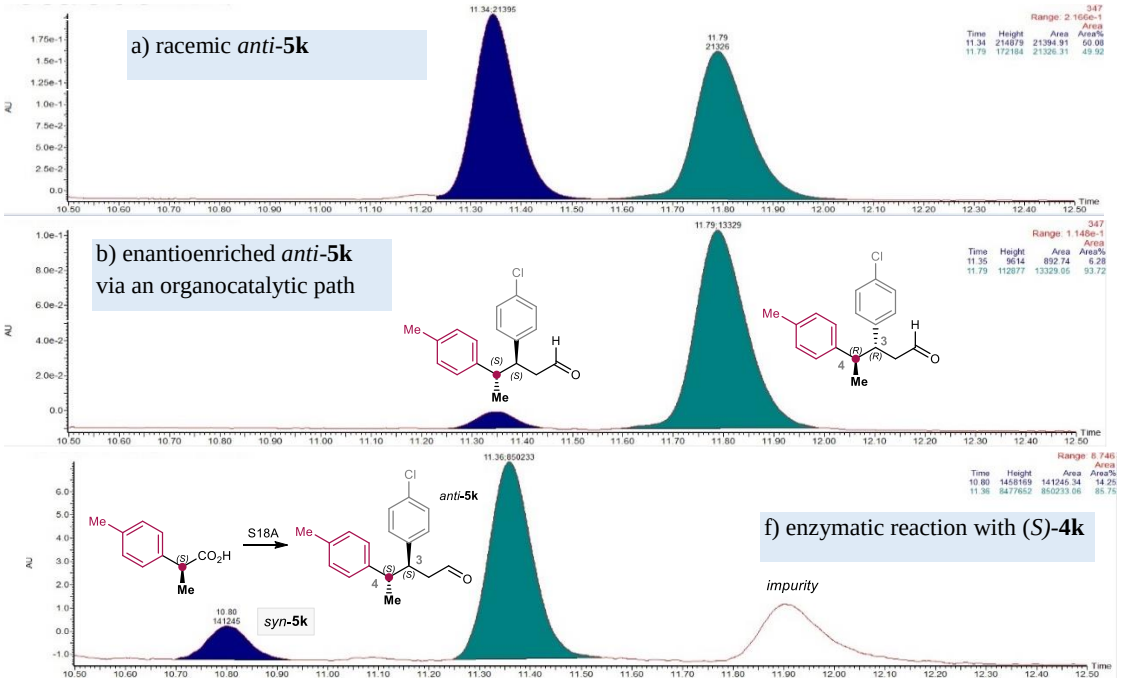
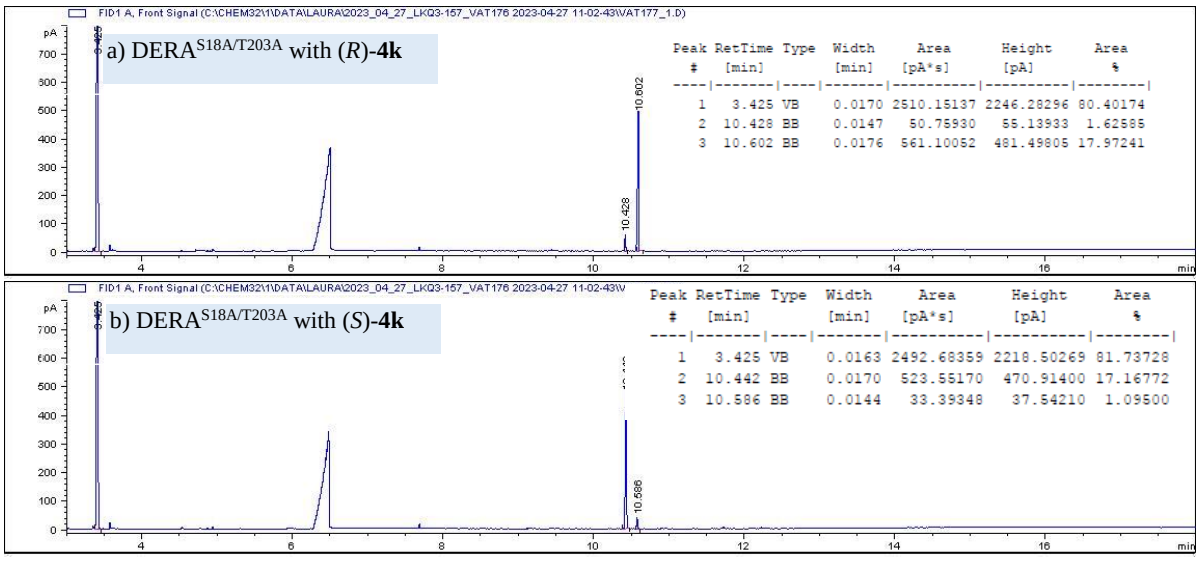


Figure S14. UPC analysis of (**a**) racemic *anti*-**5k**, (**b**) enantioenriched *anti*-**5k** prepared via the organocatalytic route with catalyst **A-1**, (**c**) *anti*-**5k** prepared via the enzymatic reactions performed with DERA^{S18A} using (*S*)-**4k**.

Determination of the conversion of 5k

The enzymatic reactions catalyzed by DERA$^{S18A/T203A}$ afforded *syn*-**5k** starting from the enantiopure chiral acid (*R*)-**4k** in 39% conversion (analytical yield) and 7.6:1 dr (**Figure S15**, top). The *anti*-**5k** product was obtained in the enzymatic reaction from (*S*)-**4k** in 48% conversion (analytical yield) and 22:1 dr (**Figure S15**, middle). These values were calculated based on the calibration curves reported in **Figure S15**, lower panel.



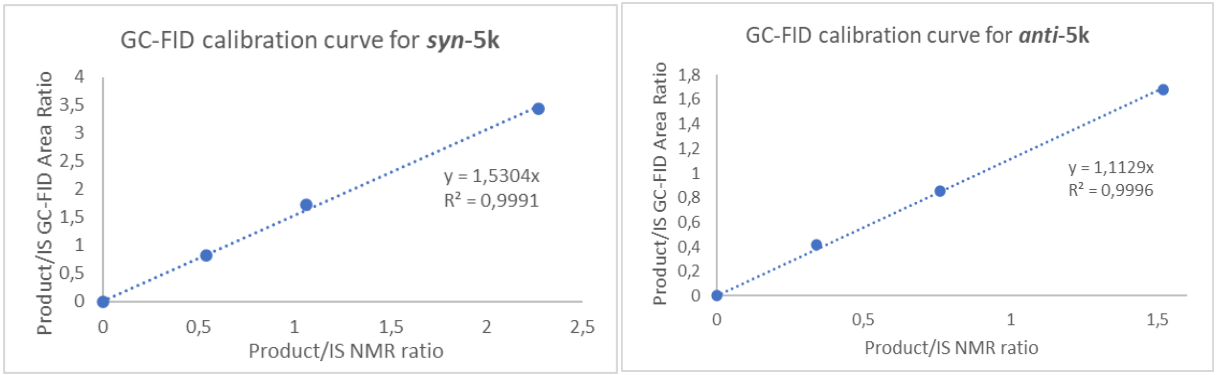
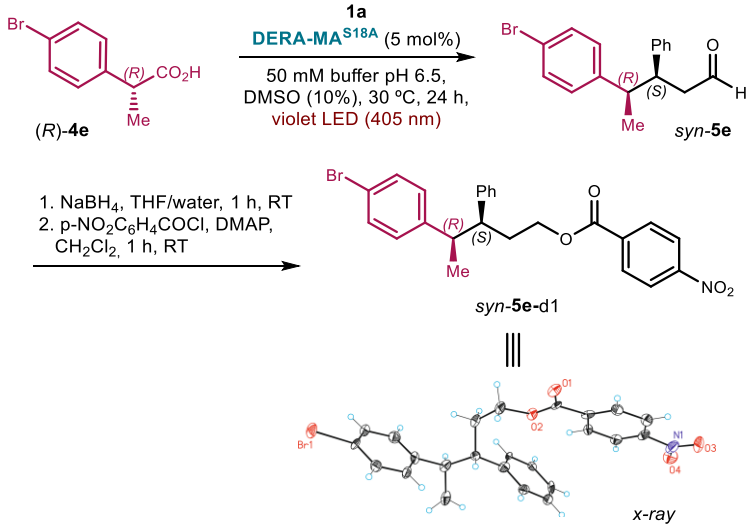


Figure S15. GC-FID analysis the enzymatic reaction performed with DERA$^{S18A/T203A}$ using (*R*)-**4k** (top) or (*S*)-**4k** (middle panel) affording *syn*-**5k** or *anti*-**5k**, respectively. GC-FID calibration curves (lower panel) for *syn*-**5k** and *anti*-**5k** were obtained from 5mM solutions of the internal standard (IS = mesitylene) in ethyl acetate with different concentrations of the corresponding **5k**.

F.3 Crystallization of a Derivative of the Enzymatically Obtained Product 5e

To confirm the stereochemical course of the reaction directly from a product obtained from the enzymatic reaction, we conducted the crystallization of a derivative from adduct *syn*-**5e**. This product was obtained from the reaction between (*R*)-**4e** and cinnamaldehyde **1a** using DERA-MA^{S18A}, following the procedure described below.



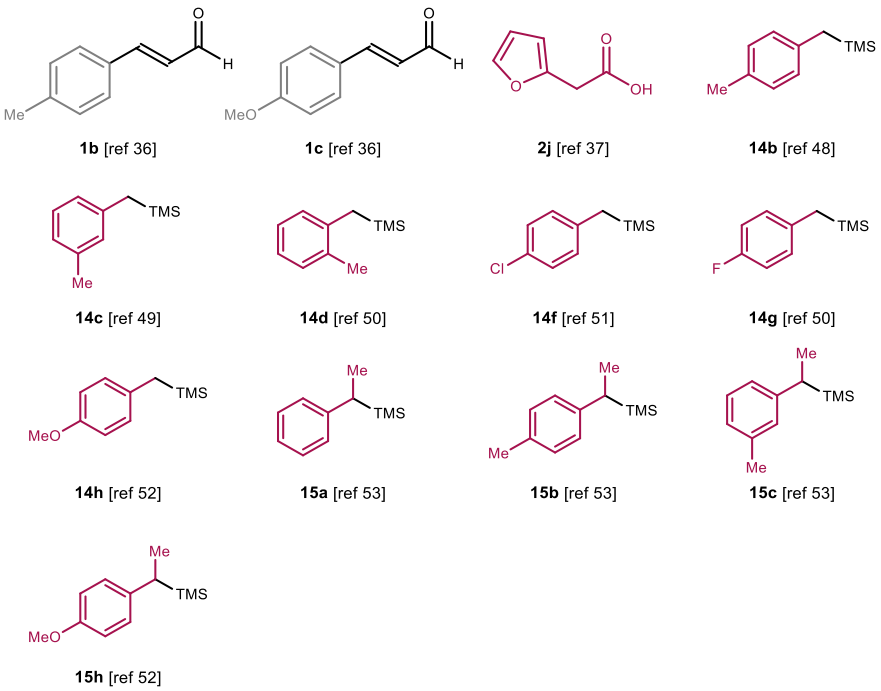
Aldehyde *syn*-**5e** was synthesized using DERA-MA^{S18A} as biocatalyst. Isolation of the ***major*** diastereoisomer by column chromatography (silica gel, 5% EtOAc in hexanes) afforded diastereopure product *syn*-**5e**.

*To facilitate the crystallization process, a reduction and esterification sequence of syn-**5e** was performed as following: a*ldehyde *syn*-**5e** (1 eq., 7.5 mg, 23.0 µmol) was dissolved in THF/water (0.5 mL, 4:1) and cooled to 0 °C using an ice bath. Then, $NaBH_4$ (10 eq., 0.23 mmol, 8.7 mg) was added portion wise, the ice bath was removed and the mixture was stirred for 30 min. After cooling to 0 °C again, excessive reductant was carefully quenched by dropwise addition of 1 N HCl until gas evolution ceased. Water (0.5 mL) was added, and the mixture was extracted with DCM (3x10 mL). The combined organic layers were dried with $MgSO_4$ and concentrated. The crude alcohol was dissolved in CH_2Cl_2 (anhydrous, 0.2 mL) and *p*-$NO_2C_6H_4Cl$ (5 eq, 21.3 mg, 115.0 µmol) and DMAP (3 eq., 8.4 mg, 69.0 µmol) were added. The mixture was stirred for 1 h at RT and directly loaded on prepTLC (30% EtOAc in hexanes), which afforded 8.0 mg of ester derivative *syn*-**5e**-d1. The compound was then directly crystallized by slow evaporation from diethylether/hexane in the refrigerator (5 ºC).

The *x-ray* crystallographic analysis (see section **K.2** for details, confirmed the (3*S*,4*R*) absolute configuration, in analogy to product *syn*-**5k**.

G. Synthesis of the Starting Material

The following compounds were prepared according to procedures described in the literature:



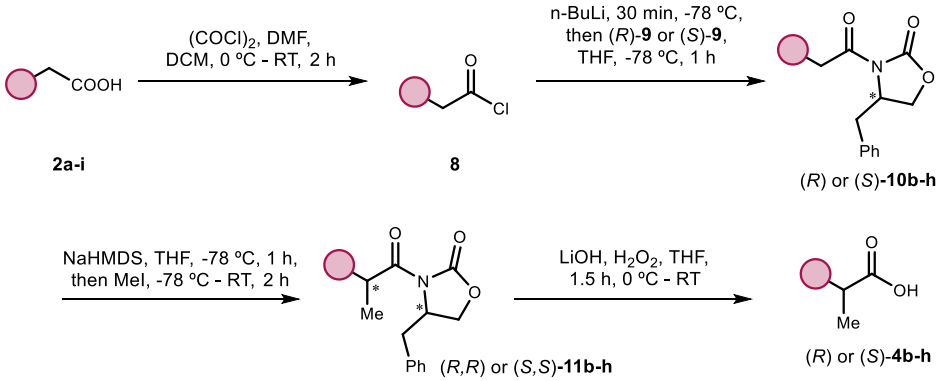
1b [ref 36] **1c** [ref 36] **2j** [ref 37] **14b** [ref 48]

14c [ref 49] **14d** [ref 50] **14f** [ref 51] **14g** [ref 50]

14h [ref 52] **15a** [ref 53] **15b** [ref 53] **15c** [ref 53]

15h [ref 52]

GP1 – General Procedure for the Synthesis of Chiral Acids 4b-4h



2a-i **8** (*R*) or (*S*)-**10b-h**

(*R,R*) or (*S,S*)-**11b-h** (*R*) or (*S*)-**4b-h**

GP1.1 – General procedure for Preparation of Acid Chlorides 8

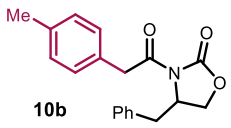
Carboxylic acid **2** (1 equiv.) was placed in a dry flask equipped with a stirring bar under Argon atmosphere. Anhydrous DCM (0.08 M) was added and the mixture was cooled to 0 °C. Oxalylchloride (1.05 equiv.) was added, followed by a drop of anhydrous DMF. Then, the ice bath was removed and the mixture was stirred until gas evolution ceased (approx. 2 hours). The mixture was concentrated under reduced pressure and the acid chlorides **8** were used without further purification.

GP1.2 – General procedure for the Synthesis of Amides 10

(R)- or *(S)*-Oxazolidinone **9** (1.05 equiv.) were placed in a dry flask under Argon atmosphere. After addition of anhydrous THF (0.3 M) the mixture was cooled to -78 °C and *n*-BuLi (1.05 equiv., 1.6 N in hexanes) was added dropwise and stirred vigorously for 30 minutes. A solution of acid chloride **8** in THF was added dropwise and the mixture was stirred for another 60 minutes at -78 °C. The ice bath was removed and the reaction mixture was allowed to warm to RT and

then quenched with NH_4Cl (sat., 20 mL). The mixture was extracted with EtOAc (3 x 30 mL), the combined organic layers were dried with $MgSO_4$ and concentrated. Purification by column chromatography (silica gel, EtOAc/hexanes) afforded the clean product **10**.

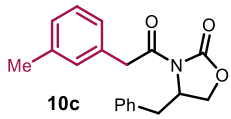
***(R)*- or *(S)*- 4-Benzyl-3-(2-(*p*-tolyl)acetyl)oxazolidin-2-one (10b)**



(R)- or *(S)*-**6p** was prepared according to ***GP1.1* / *GP1.2***, using carboxylic acid **2b** (901 mg. 6.0 mmol), oxalylchloride (540 µL, 6.3 mmol), *(R)*- or *(S)*- 4-benzyl-2-oxazolidinone (1.12 g, 6.3 mmol) and *n*-BuLi (1.6 N, 3.94 mL, 6.3 mmol). Purification with 10% EtOAc in hexanes afforded 1.01 g (54%) for *(R)*-**10b** and 1.37 g (74%) for *(S)*-**10b**. The characterization of the title compound was consistent with the data available in the literature (*39*).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 – 7.26 (m, 2H), 7.24 – 7.23 (m, 2H), 7.15 – 7.12 (m, 4H), 4.67 (ddt, *J* = 9.4, 7.0, 3.4 Hz, 1H), 4.34 – 4.14 (m, 3H), 3.27 (dd, *J* = 13.4, 3.3 Hz, 1H), 2.75 (dd, *J* = 13.4, 9.5 Hz, 1H), 2.35 (s, 3H).

***(R)*- or *(S)*- 4-Benzyl-3-(2-(m-tolyl)acetyl)oxazolidin-2-one (10c)**



(R)- or *(S)*-**10c** was prepared according to ***GP1.1* / *GP1.2***, using carboxylic acid **2c** (300.3 mg. 2.0 mmol,), oxalylchloride (180 µL, 2.1 mmol), *(R)*- or *(S)*- 4-benzyl-2-oxazolidinone (372.0 mg, 2.1 mmol) and *n*-BuLi (1.6 N, 1.31 mL, 2.1 mmol). Purification with 20% EtOAc in hexanes afforded 312 mg (50%) for *(R)*-**10c** and 348 mg (56%) for *(S)*-**10c**.

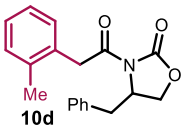
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 – 7.22 (m, 4H), 7.17 – 7.09 (m, 5H), 4.71 – 4.64 (m, 1H), 4.30 (d, *J* = 15.6 Hz, 1H), 4.24 (d, *J* = 15.6 Hz, 1H), 4.23 – 4.16 (m, 2H), 3.28 (dd, *J* = 13.4, 3.3 Hz, 1H), 2.76 (dd, *J* = 13.4, 9.5 Hz, 1H), 2.36 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 171.51, 153.55, 138.38, 135.30, 133.51, 130.67, 129.58, 129.09, 128.63, 128.18, 127.49, 126.94, 66.26, 55.51, 41.63, 37.91, 21.56.

HRMS (ESI): calculated for $[M+Na]^+$ $C_{19}H_{19}NNaO_3$: 332.1257, found: 332.1266.

$[\alpha]_D^{20}$ (*(S)*-**6q**) = +56.2 (c = 0.5, $CHCl_3$).

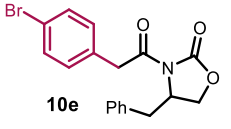
***(R)*- or *(S)*- 4-Benzyl-3-(2-(o-tolyl)acetyl)oxazolidin-2-one (10d)**



(R)- or *(S)*-**10d** was prepared according to ***GP1.1* / *GP1.2***, using carboxylic acid **2d** (300.3 mg. 2.0 mmol,), oxalylchloride (180 µL, 2.1 mmol), *(R)*- or *(S)*- 4-benzyl-2-oxazolidinone (372.0 mg, 2.1 mmol) and *n*-BuLi (1.6 N, 1.31 mL, 2.1 mmol). Purification with 20-30% EtOAc in hexanes to afford 509 mg (82%) for *(R)*-**10d** and 493 mg (80%) for *(S)*-**10d**, which was already described in the literature (*40*).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 – 7.27 (m, 3H), 7.23 – 7.17 (m, 6H), 4.70 (m, 1H), 4.38 – 4.18 (m, 4H), 3.33 (dd, *J* = 13.3, 3.3 Hz, 1H), 2.78 (dd, *J* = 13.3, 9.7 Hz, 1H), 2.31 (s, 3H).

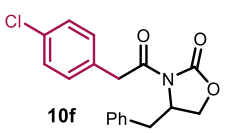
***(R)*- *or (S)*-4-Benzyl-3-(2-(4-bromophenyl)acetyl)oxazolidin-2-one (10e)**



(R)- *or (S)*-**10e** was prepared according to ***GP1.1* / *GP1.2***, using carboxylic acid **2e** (430.1 mg. 2.0 mmol,), oxalylchloride (180 µL, 2.1 mmol), *(R)*- or *(S)*- 4-benzyl-2-oxazolidinone (372.0 mg, 2.1 mmol) and *n*-BuLi (1.6 N, 1.31 mL, 2.1 mmol). Purification with 20-40% EtOAc in hexanes to afford 546 mg (73%) for *(R)*-**10e** and 493 mg (66%) for *(S)*-**10e**. **10e** was already described in the literature (*41*).

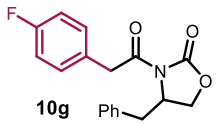
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.5 Hz, 2H), 7.35 – 7.18 (m, 5H), 7.17 – 7.10 (m, 2H), 4.73 – 4.62 (m, 1H), 4.30 (d, *J* = 15.7 Hz, 1H), 4.25 – 4.16 (m, 3H), 3.26 (dd, *J* = 13.4, 3.2 Hz, 1H), 2.76 (ddd, *J* = 13.4, 9.4, 0.0 Hz, 1H).

***(R)- or (S)*-4-Benzyl-3-(2-(4-chlorophenyl)acetyl)oxazolidin-2-one (10f)**



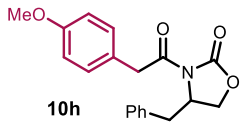
(R)- or (S)-**10f** was prepared according to ***GP1.1* / *GP1.2***, using carboxylic acid **2f** (341.2 mg. 2.0 mmol,), oxalylchloride (180 µL, 2.1 mmol), *(R)*- or *(S)*- 4-benzyl-2-oxazolidinone (372.0 mg, 2.1 mmol) and *n*-BuLi (1.6 N, 1.31 mL, 2.1 mmol). Purification with 20-30% EtOAc in hexanes afforded 475 mg (72%) for *(R)*-**10f** and 453 mg (69%) for *(S)*-**10f**. **10f** was already described in the literature (*42*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 – 7.23 (m, 7H), 7.16 – 7.11 (m, 2H), 4.72 – 4.64 (m, 1H), 4.32 (d, *J* = 15.7 Hz, 1H), 4.26 – 4.16 (m, 3H), 3.26 (dd, *J* = 13.4, 3.4 Hz, 1H), 2.76 (dd, *J* = 13.4, 9.4 Hz, 1H).

***(R)- or (S)*-4-Benzyl-3-(2-(4-fluorophenyl)acetyl)oxazolidin-2-one (10g)**



(R)- or (S)-**10g** was prepared according to ***GP1.1* / *GP1.2***, using carboxylic acid **2g** (308.3 mg. 2.0 mmol,), oxalylchloride (180 µL, 2.1 mmol), *(R)*- or *(S)*- 4-benzyl-2-oxazolidinone (372.0 mg, 2.1 mmol) and *n*-BuLi (1.6 N, 1.31 mL, 2.1 mmol). Purification with 20-30% EtOAc in hexanes afforded 492 mg (70%) for *(R)*-**10g** and 581 mg (93%) for *(S)*-**10g**. **10g** was already described in the literature (*43*). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.22 (m, 5H), 7.17 – 7.10 (m, 2H), 7.09 – 6.99 (m, 2H), 4.73 – 4.63 (m, 1H), 4.32 (d, *J* = 15.8 Hz, 1H), 4.26 – 4.16 (m, 3H), 3.26 (dd, *J* = 13.4, 3.3 Hz, 1H), 2.76 (dd, *J* = 13.4, 9.5 Hz, 1H).

***(R)- or (S)*-4-Benzyl-3-(2-(4-methoxyphenyl)acetyl)oxazolidin-2-one (10h)**



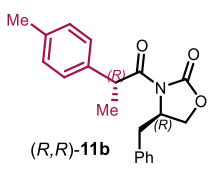
(R)- or (S)-**10h** was prepared according to ***GP1.1* / *GP1.2***, using carboxylic acid **2h** (332.4 mg. 2.0 mmol,), oxalylchloride (180 µL, 2.1 mmol), *(R)*- or *(S)*- 4-benzyl-2-oxazolidinone (372.0 mg, 2.1 mmol) and *n*-BuLi (1.6 N, 1.31 mL, 2.1 mmol). Purification with 30-40% EtOAc in hexanes to afford 653 mg (quant) for *(R)*-**10h** and 620 mg (95%) for *(S)*-**10h. 10h** was already described in the literature (*44*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.21 (m, 5H), 7.17 – 7.10 (m, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 4.72 – 4.62 (m, 1H), 4.28 (d, *J* = 15.7 Hz, 1H), 4.24 – 4.16 (m, 3H), 3.81 (s, 3H), 3.27 (dd, *J* = 13.4, 3.3 Hz, 1H), 2.76 (ddd, *J* = 13.4, 9.5, 0.0 Hz, 1H).

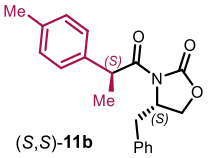
***GP1.3* – General procedure for methylation of amide 10 – Synthesis of 11**

Amide (1 equiv.) was placed in a dry flask, dissolved in anhydrous THF (0.1 M) and cooled to -78 °C under Argon atmosphere. Then, a solution of NaHMDS (1.2 equiv., 1 N in THF) was added and the mixture was stirred for 1 h. Then, methyl iodide (5 equiv.) was added and the mixture was stirred for 2 h. The ice bath was removed, the mixture was stirred overnight and then concentrated under reduced pressure. The crude products were purified by column chromatography (SiO_2, hexane:ethyl acetate 8:2) and only pure fractions were isolated to ensure diastereopure products.

***(R,R)*- or *(S,S)*-4-Benzyl-3-(-2-(p-tolyl)propanoyl)oxazolidin-2-one (11b)**



(R,R)-**11b**: The reaction was performed according to ***GP1.3*** using *(R)*-**10b** (1.01 g, 3.26 mmol), NaHMDS (5.3 mL, 5.3 mmol) and MeI (1.01 mL, 16.3 mmol) to afford 743 mg (70%) of *(R,R)*-**11b.** The characterization of **11b** was consistent with the data available in the literature (39).

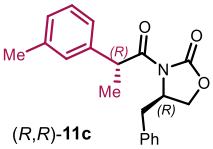


(*S,S*)-**11b**

(*S,S*)-**11b**: The reaction was performed according to ***GP1.3*** using *(S)*-**10b** (1.37 g, 4.4 mmol), NaHMDS (3.6 mL, 3.6 mmol) and MeI (1.37 mL, 22.0 mmol) to afford 1.14 g (79%)of *(S,S)*-**11b.**

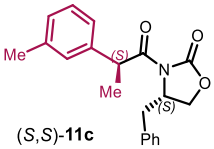
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 2H), 7.30 – 7.25 (m, 3H), 7.24 – 7.19 (m, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 5.09 (q, *J* = 7.0 Hz, 1H), 4.58 (dddd, *J* = 9.8, 7.6, 3.3, 2.4 Hz, 1H), 4.13 – 4.01 (m, 2H), 3.35 (dd, *J* = 13.3, 3.3 Hz, 1H), 2.80 (dd, *J* = 13.3, 9.8 Hz, 1H), 2.32 (s, 3H), 1.53 (d, *J* = 7.0 Hz, 3H).

***(R,R)*- or *(S,S)*-4-Benzyl-3-(-2-(m-tolyl)propanoyl)oxazolidin-2-one (11c)**



(*R,R*)-**11c**

(*R,R*)-**11c:** The reaction was performed according to ***GP1.3*** using *(R)*-**10c** (312 mg, 1.00 mmol), NaHMDS (1.1 mL, 1.1 mmol) and MeI (0.31 mL, 5.0 mmol) to afford 137 mg (42%) of *(R,R)*-**11c.**



(*S,S*)-**11c**

(*S,S*)-**11c:** The reaction was performed according to ***GP1.3*** using *(S)*-**10c** (348 mg, 1.06 mmol), NaHMDS (1.17 mL, 1.17 mmol) and MeI (0.32 mL, 5.3 mmol) to afford 169 mg (49%) of *(S,S)*-**11c**.

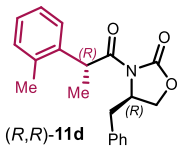
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (dd, *J* = 8.1, 6.6 Hz, 2H), 7.30 – 7.27 (m, 1H), 7.24 – 7.15 (m, 5H), 7.06 (d, *J* = 7.2 Hz, 1H), 5.10 (q, *J* = 7.0 Hz, 1H), 4.11 (dd, *J* = 9.1, 2.4 Hz, 1H), 4.09 – 4.04 (m, 1H), 3.36 (dd, *J* = 13.3, 3.3 Hz, 1H), 2.80 (dd, *J* = 13.3, 9.8 Hz, 1H), 2.34 (s, 3H), 1.54 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.89, 153.06, 140.32, 138.42, 135.54, 129.59, 129.11, 128.94, 128.65, 128.19, 127.50, 125.32, 66.01, 56.00, 43.14, 38.10, 21.58, 19.61.

HRMS (ESI): calculated for $[M+Na]^+$ $[C_{20}H_{21}NNaO_3]^+$: 346.1414; found: 346.1407.

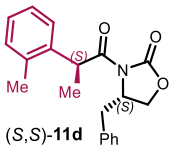
$[\alpha]_D^{20}$ (*(S)*-**11c**) = +98.9 (c = 0.5, $CHCl_3$).

***(R,R)*- or *(S,S)*-4-Benzyl-3-(-2-(o-tolyl)propanoyl)oxazolidin-2-one (11d)**



(*R,R*)-**11d**

(*R,R*)-**11d**: The reaction was performed according to ***GP1.3*** using *(R)*-**10d** (509 mg, 1.64 mmol), NaHMDS (1.8 mL, 1.8 mmol) and MeI (0.51 mL, 8.2 mmol) to afford 361 mg (68%) of *(R,R)*-**11d**.



(*S,S*)-**11d**

(*S,S*)-**11d:** The reaction was performed according to ***GP1.3*** using *(S)*-**10d** (493 mg, 1.60 mmol), NaHMDS (1.76 mL, 1.76 mmol) and MeI (0.50 mL, 8.0 mmol) to afford 449 mg (87%) of *(S,S)*-**11d**.

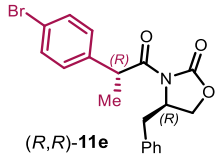
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.32 (m, 2H), 7.31 – 7.22 (m, 3H), 7.19 – 7.12 (m, 4H), 5.16 (q, J = 6.9 Hz, 1H), 4.70 – 4.60 (m, 1H), 4.11 (dd, J = 9.1, 2.4 Hz, 1H), 4.08 – 4.03 (m, 1H), 3.39 (dd, J = 13.3, 3.3 Hz, 1H), 2.80 (dd, J = 13.3, 9.8 Hz, 1H), 2.42 (s, 3H), 1.47 (d, J = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.06, 152.92, 139.18, 136.63, 135.56, 130.87, 129.59, 129.11, 127.49, 127.16, 126.42, 125.72, 66.07, 56.13, 40.83, 38.10, 19.41, 18.34.

HRMS (ESI): calculated for $[M+Na]^+$ $[C_{20}H_{21}NNaO_3]^+$: 346.1414, found: 346.1402.

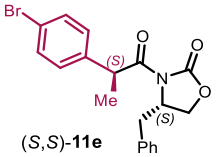
$[\alpha]_D^{20}$ (*(S)*-**11d**) = +160.3 (c = 0.5, $CHCl_3$).

***(R,R)*- or *(S,S)*-4-Benzyl-3-(-2-(4-bromophenyl)propanoyl)oxazolidin-2-one (11e)**



(*R,R*)-**11e**

(R,R)-**11e:** The reaction was performed according to ***GP1.3*** using *(R)*-**10e** (546 mg, 1.46 mmol), NaHMDS (1.61 mL, 1.161 mmol) and MeI (0.45 mL, 7.3 mmol) to afford 404 mg (71%) of *(R,R)*-**11e**. **11e** is already described in the literature (*41*).

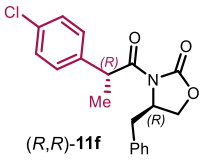


(*S,S*)-**11e**

(S,S)-**11e:** The reaction was performed according to ***GP2.3*** using *(S)*-**10e** (493 mg, 1.32 mmol), NaHMDS (1.45 mL, 1.45 mmol) and MeI (0.41 mL, 6.6 mmol) to afford 426 mg (83%) of *(S,S)*-**11e**.

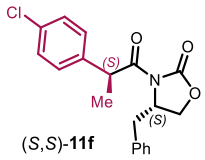
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.5 Hz, 2H), 7.38 – 7.17 (m, 7H), 5.08 (q, *J* = 7.0 Hz, 1H), 4.64 – 4.54 (m, 1H), 4.13 (dd, *J* = 9.1, 2.6 Hz, 1H), 4.10 – 4.05 (m, 1H), 3.34 (dd, *J* = 13.3, 3.3 Hz, 1H), 2.80 (dd, *J* = 13.3, 9.7 Hz, 1H), 1.53 (d, *J* = 7.0 Hz, 3H).

***(R,R)*- or *(S,S)*-4-Benzyl-3-(-2-(4-chlorophenyl)propanoyl)oxazolidin-2-one (11f)**



(*R,R*)-**11f**

(R,R)-**11f:** The reaction was performed according to ***GP1.3*** using *(R)*-**10f** (475 mg, 1.44 mmol), NaHMDS (1.58 mL, 1.58 mmol) and MeI (0.45 mL, 7.2 mmol) to afford 324 mg (65%) of *(R,R)*-**11f**. **11f** is already described in the literature (*45*).

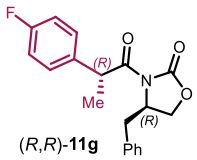


(*S,S*)-**11f**

(S,S)-**11f:** The reaction was performed according to ***GP1.3*** using *(S)*-**10f** (453 mg, 1.38 mmol), NaHMDS (1.52 mL, 1.52 mmol) and MeI (0.43 mL, 6.9 mmol) to afford 384 mg (81%) of *(S,S)*-**11f**.

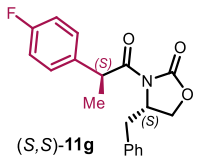
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.27 (m, 7H), 7.24 – 7.20 (m, 2H), 5.09 (q, *J* = 7.0 Hz, 1H), 4.64 – 4.54 (m, 1H), 4.17 – 4.04 (m, 2H), 3.34 (dd, *J* = 13.3, 3.3 Hz, 1H), 2.80 (dd, *J* = 13.3, 9.7 Hz, 1H), 1.56 – 1.50 (m, 3H).

***(R,R)*- or *(S,S)*-4-Benzyl-3-(-2-(4-fluorophenyl)propanoyl)oxazolidin-2-one (11g)**



(*R,R*)-**11g**

(R,R)-**11g:** The reaction was performed according to ***GP1.3*** using *(R)*-**10g** (492 mg, 1.56 mmol), NaHMDS (1.72 mL, 1.72 mmol) and MeI (0.48 mL, 7.8 mmol) to afford 250 mg (49 %) of *(R,R)*-**11g**.



(*S,S*)-**11g**

(S,S)-**11g:** The reaction was performed according to ***GP1.3*** using *(S)*-**10g** (581 mg, 1.86 mmol), NaHMDS (2.05 mL, 2.05 mmol) and MeI (0.58 mL, 9.3 mmol) to afford 249 mg (41%) of *(S,S)*-**11g**.

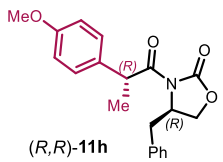
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.27 (m, 5H), 7.24 – 7.20 (m, 2H), 7.00 (t, *J* = 8.7 Hz, 2H), 5.11 (q, *J* = 7.0 Hz, 1H), 4.64 – 4.56 (m, 1H), 4.13 (dd, *J* = 9.1, 2.6 Hz, 1H), 4.11 – 4.05 (m, 1H), 3.34 (dd, *J* = 13.3, 3.3 Hz, 1H), 2.80 (dd, *J* = 13.3, 9.7 Hz, 1H), 1.53 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.68, 162.19 (d, *J* = 245.8 Hz), 153.07, 136.05 (d, *J* = 3.2 Hz), 135.39, 129.88 (d, *J* = 8.0 Hz), 129.56, 129.13, 127.55, 115.60 (d, *J* = 21.3 Hz), 66.10, 55.91, 42.49, 38.08, 19.67.

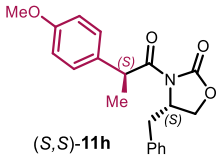
HRMS (ESI): calculated for $[M+Na]^+$ $[C_{19}H_{18}FNNaO_3]^+$: 350.1163, found: 350.1159.

$[\alpha]_D^{20}$ (***(S)*-11g**) = +91.2 (c = 0.5, $CHCl_3$).

***(R,R)*- or *(S,S)*-4-Benzyl-3-(-2-(4-methoxyphenyl)propanoyl)oxazolidin-2-one (11h)**



(R,R)-**11h:** The reaction was performed according to ***GP1.3*** using *(R)*-**10h** (653 mg, 2.00 mmol), NaHMDS (2.2 mL, 2.2 mmol) and MeI (0.62 mL, 10.0 mmol) to afford 142 mg (21%) of *(R,R)*-**11h**.



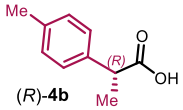
(S,S)-**11h:** The reaction was performed according to ***GP1.3*** using *(S)*-**10h** (620 mg, 1.90 mmol), NaHMDS (2.1 mL, 2.1 mmol) and MeI (0.59 mL, 9.5 mmol) to afford 156 mg (24%) of *(S,S)*-**11h**.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.19 (m, 7H), 6.85 (d, *J* = 8.9 Hz, 2H), 5.07 (q, *J* = 7.0 Hz, 1H), 4.63 – 4.53 (m, 1H), 4.11 (dd, *J* = 9.1, 2.5 Hz, 1H), 4.08 – 4.03 (m, 1H), 3.78 (s, 3H), 3.35 (dd, *J* = 13.3, 3.3 Hz, 1H), 2.80 (dd, *J* = 13.3, 9.7 Hz, 1H), 1.52 (d, *J* = 7.0 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$): δ 175.09, 158.94, 153.08, 135.52, 132.48, 129.58, 129.33, 129.10, 127.49, 114.16, 77.48, 77.16, 76.84, 66.03, 55.97, 55.39, 42.35, 38.11, 19.60.
HRMS (ESI): calculated for $[M+Na]^+$ $[C_{20}H_{21}NNaO_4]^+$: 362.1363, found: 362.1352.
$[\alpha]_D^{20}$ (***(S)*-11h**) = +93.1 (c = 0.5, $CHCl_3$).

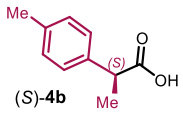
***GP1.4* – General Procedure for Hydrolysis of Amide 11 – Synthesis of 4**

The following modified procedure was adopted from a literature procedure (*9*). Amide **11** (1 equiv.) was dissolved in a mixture of THF (5 mL per mmol amide) and water (2 mL per mmol amide) and cooled to 0 ºC. Then, H_2O_2 (30% in water, 4 equiv.) and LiOH • H_2O (1 N in water, 3 equiv.) was added and the mixture was stirred vigorously for 1 h. The ice bath was removed and attired for another 30 minutes. The mixture was quenched with $Na_2S_2O_3$ (1mL, 10% in water) and 5 mL of water was added. The mixture was extracted with ethyl acetate (20 mL, discard layer), the aqueous layer was acidified to pH = 2 with aqueous 1N HCl and extracted with DCM (3x 20 mL). The combined DCM fractions were dried with $MgSO_4$ and purified by flash column chromatography (SiO_2, hexane:EtOAc 1:1) to afford the pure product **4**.

2-(*p*-Tolyl)propanoic acid (4b)



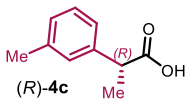
(R)-**4b**: The reaction was performed according to ***GP1.4*** using *(R,R)*-**11b** (743 mg, 2.30 mmol), H_2O_2 (30%, 0.93 mL) and LiOH (1 M, 6.9 mL, 6.9 mmol) to afford 318 mg (84%) of *(R)*-**4b**. **4b** is already described in the literature (*46*).



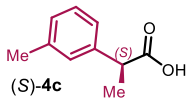
(S)-**4b**: The reaction was performed according to ***GP1.4*** using *(S,S)*-**11b** (1.14 g, 3.51 mmol), H_2O_2 (30%, 1.43 mL) and LiOH (1 M, 10.5 mL, 10.5 mmol) to afford 431 mg (75%) of *(S)*-**4b.**

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 8.1 Hz, 2H), 3.71 (q, *J* = 7.2 Hz, 1H), 2.33 (s, 3H), 1.50 (d, *J* = 7.2 Hz, 3H).
$[\alpha]_D^{20}$ (***(S)*-4b**) = +66.5 (c = 0.11, CH_2Cl_2).

2-(*m*-Tolyl)propanoic acid (4c)



(R)-**4c**: The reaction was performed according to ***GP1.4*** using *(R,R)*-**11c** (137 mg, 0.42 mmol), H_2O_2 (30%, 0.17 mL) and LiOH (1 M, 1.26 mL, 1.26 mmol) to afford 58 mg (84%) of *(R)*-**4c**. **4c** is already described in the literature (*46*).

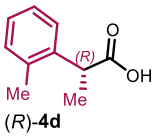


(S)-**4c**: The reaction was performed according to ***GP1.4*** using *(S,S)*-**11c** (159 mg, 0.49 mmol), H_2O_2 (30%, 0.20 mL) and LiOH (1 M, 1.47 mL, 1.47 mmol) to afford 63 mg (78%) of *(S)*-**4c**.

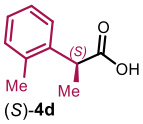
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (td, *J* = 7.4, 1.0 Hz, 1H), 7.15 – 7.05 (m, 3H), 3.71 (q, *J* = 7.2 Hz, 1H), 2.34 (s, 3H), 1.50 (d, *J* = 7.2 Hz, 3H).

$[\alpha]_D^{20}$ (*(S)*-**4c**) = +65.3 (c = 0.5, $CHCl_3$).

2-(*o*-Tolyl)propanoic acid (4d)



(R)-**4d**: The reaction was performed according to ***GP1.4*** using *(R,R)*-**11d** (361 mg, 1.12 mmol), H_2O_2 (30%, 0.45 mL) and LiOH (1 M, 3.48 mL, 3.48 mmol) to afford 163 mg (89%) of *(R)*-**4d**. **4d** is already described in the literature (*46*).

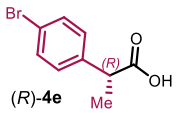


(S)-**4d**: The reaction was performed according to ***GP1.4*** using *(S,S)*-**11d** (439 mg, 1.36 mmol), H_2O_2 (30%, 0.55 mL) and LiOH (1 M, 4.05 mL, 4.05 mmol) to afford 185 mg (83%) of *(S)*-**4d**.

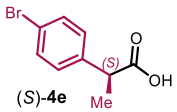
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (d, *J* = 7.3 Hz, 1H), 7.23 – 7.13 (m, 3H), 3.99 (q, *J* = 7.1 Hz, 1H), 2.38 (s, 3H), 1.50 (d, *J* = 7.1 Hz, 3H).

$[\alpha]_D^{20}$ (*(S)*-**4d**) = +83.4 (c = 0.5, $CHCl_3$).

2-(4-Bromophenyl)propanoic acid (4e)



(R)-**4e**: The reaction was performed according to ***GP1.4*** using *(R,R)*-**11e** (404 mg, 1.04 mmol), H_2O_2 (30%, 0.42 mL) and LiOH (1 M, 3.12 mL, 3.12 mmol) to afford 171.2 mg (72%) of *(R)*-**4e**. **4e** is already described in the literature (*46*).

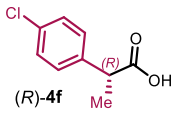


(S)-**4e**: The reaction was performed according to ***GP1.4*** using *(S,S)*-**11e** (426 mg, 1.10 mmol), H_2O_2 (30%, 0.45 mL) and LiOH (1 M, 3.33 mL, 3.33 mmol) to afford 194 mg (77%) of *(S)*-**4e**.

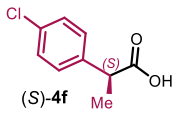
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.5 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 3.71 (q, *J* = 7.2 Hz, 1H), 1.50 (d, *J* = 7.2 Hz, 3H).

$[\alpha]_D^{20}$ (*(S)*-**4e**) = +43.4 (c = 0.5, $CHCl_3$).

2-(4-Chlorophenyl)propanoic acid (4f)



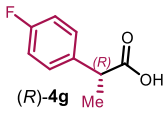
(R)-**4f**: The reaction was performed according to ***GP1.4*** using *(R,R)*-**11f** (324 mg, 0.94 mmol), H_2O_2 (30%, 0.38 mL) and LiOH (1 M, 2.82 mL, 2.82 mmol) to afford 136.9 mg (79%) of *(R)*-**4f**. **4f** is already described in the literature (*46*).



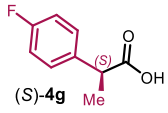
(S)-**4f**: The reaction was performed according to ***GP1.4*** using *(S,S)*-**11f** (384 mg, 1.12 mmol), H_2O_2 (30%, 0.46 mL) and LiOH (1 M, 3.33 mL, 3.33 mmol) to afford 162.3 mg (79%) of *(S)*-**4f**.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.23 (m, 4H), 3.73 (q, *J* = 7.2 Hz, 1H), 1.51 (d, *J* = 7.2 Hz, 3H). $[\alpha]_D^{20}$ (*(S)*-**4f**) = +54.7 (c = 0.5, $CHCl_3$).

2-(4-Fluorophenyl)propanoic acid (4g)



(R)-**4g**: The reaction was performed according to ***GP1.4*** using *(R,R)*-**11g** (250 mg, 0.76 mmol), H_2O_2 (30%, 0.31 mL) and LiOH (1 M, 2.28 mL, 2.28 mmol) to afford 108.9 mg (85%) of *(R)*-**4g**. **4g** is already described in the literature (*46*).

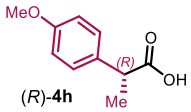


(S)-**4g**: The reaction was performed according to ***GP1.4*** using *(S,S)*-**11g** (239 mg, 0.73 mmol), H_2O_2 (30%, 0.30 mL) and LiOH (1 M, 2.19 mL, 2.19 mmol) to afford 87.8 mg (71%) of *(S)*-**4g**.

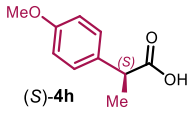
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.27 (m, 2H), 7.02 (t, *J* = 8.6 Hz, 2H), 3.74 (q, *J* = 7.2 Hz, 1H), 1.51 (d, *J* = 7.2 Hz, 3H).

$[\alpha]_D^{20}$ (*(S)*-**4g**) = +53.6 (c = 0.5, $CHCl_3$).

2-(4-Methoxyphenyl)propanoic acid (4h)



(R)-**4h**: The reaction was performed according to ***GP1.4*** using *(R,R)*-**11h** (142 mg, 0.42 mmol), H_2O_2 (30%, 0.17 mL) and LiOH (1 M, 1.26 mL, 1.26 mmol) to afford 58.8 mg (78%) of *(R)*-**4h**. **4h** is already described in the literature (*46*).



(S)-**4h**: The reaction was performed according to ***GP1.4*** using *(S,S)*-**11h** (146 mg, 0.43 mmol), H_2O_2 (30%, 0.18 mL) and LiOH (1 M, 1.29 mL, 1.29 mmol) to afford 59.5 mg (77%) of *(S)*-**4h**.

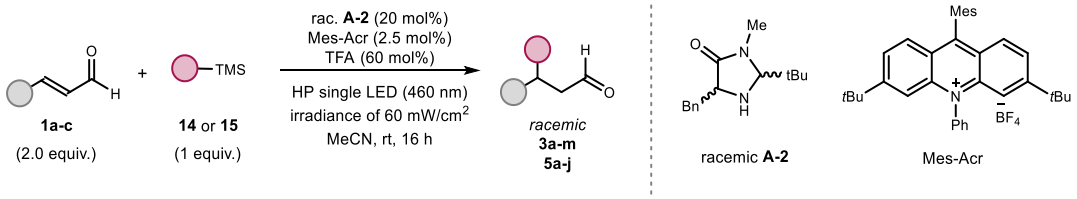
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 – 7.23 (m, 2H), 6.90 – 6.84 (m, 2H), 3.79 (s, 3H), 3.70 (q, *J* = 7.2 Hz, 1H), 1.50 (d, *J* = 7.2 Hz, 3H). $[\alpha]_D^{20}$ (*(S)*-**4h**) = +56.1 (c = 0.5, $CHCl_3$).

H. Reference Compounds Synthesis

The reference compounds described in this section were used to determine the response factor for quantifying the conversion to the products (analytical yield) of the photoenzymatic processes through GC-FID analysis. Additionally, they were used as racemic samples for determining the enantiomeric excess through UPC^2 analysis. The samples were prepared using organocatalytic protocols, which typically resulted in mixtures of diastereoisomers.

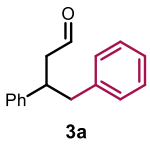
H.1 Synthesis and Characterization of Reference Compounds 3 and 5

***GP2* – General Procedure for the Organocatalyzed Synthesis of the Racemic Reference Compounds 3 and 5**



Reference compounds **3** and **5** were synthesized following a reported literature procedure (*34*). To a 5 mL argon-purged glass vial, containing a racemic mixture (mixing (*R*,*R*) and (*S*,*S*) in a 1:1 ratio) of the amine catalyst **A-2** (0.04 mmol, 0.2 equiv.), the photocatalyst Mes-Acr (5.0 µmol, 2.5 mol%) and the silane **14** or **15** (0.2 mmol, 1 equiv.), enal **1** (0.4 mmol, 2 equiv.) was added. Then, 400 µL of an argon-sparged 0.3 M acetonitrile solution of TFA (9.2 µL, 0.12 mmol, 60 mol%) was added. The vial was sealed with Parafilm, and then placed into a 3D-printed holder, fitted with a 460 nm high-power single LED. The irradiance was fixed at 60±2 mW/cm^2, as controlled by an external power supply and measured using a photodiode light detector at the start of each reaction. This setup secured a reliable irradiation while keeping a distance of 1 cm between the reaction vessel and the light source. The reaction was stirred at room temperature for 16 h, then the solvent was evaporated and the crude mixture was purified by flash column chromatography on silica gel to furnish the product **3** and **5**.

3,4-Diphenylbutanal (3a)

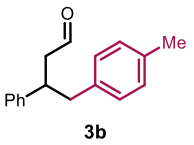


3a

Prepared according to **GP2**, using benzyltrimethylsilane **14a** (38 µL, 0.2 mmol), the racemic amine catalyst **A-2** (9.9 mg, 40 µmol), the photocatalyst Mes-Acr (2.9 mg, 5 µmol, 2.5 mol%) and cinnamaldehyde **1a** (51 µL, 0.4 mmol) in 0.3 M acetonitrile solution of TFA (9.2 µL, 0.12 mmol, 60 mol%). The solution was irradiated for 16h at room temperature. The crude mixture was purified by flash column chromatography (SiO_2, hexane:Et_2O 95:5, two consecutive purifications) to afford racemic product **3a** (31.4 mg, 0.14 mmol, 70% yield) as colorless oil. The enantiomers of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) were separated by UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/*i*-PrOH for 5 min; isocratic 60:40 CO_2/*i*-PrOH for 2 min, gradient from 60:40 CO_2/*i*-PrOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 347 nm, **3a**: τ = 6.4 min and τ = 6.6 min. The characterization of the title compound was consistent with the data available in the literature (*24*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (t, *J* = 2.0 Hz, 1H), 7.32 – 7.26 (m, 2H), 7.26 – 7.15 (m, 6H), 7.10 – 7.04 (m, 2H), 3.51 (p, *J* = 7.7 Hz, 1H), 3.02 – 2.86 (m, 2H), 2.85 – 2.69 (m, 2H).

3-Phenyl-4-(*p*-tolyl)butanal (3b)

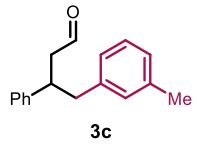


3b

Prepared according to **GP2**, using silane **14b** (41 µL, 0.2 mmol), the racemic amine catalyst **A-2** (9.9 mg, 40 µmol), the photocatalyst Mes-Acr (2.9 mg, 5 µmol, 2.5 mol%) and cinnamaldehyde **1a** (51 µL, 0.4 mmol) in 0.3 M acetonitrile solution of TFA (9.2 µL, 0.12 mmol, 60 mol%). The solution was irradiated for 16h at room temperature. The crude mixture was purified by flash column chromatography (SiO_2, hexane:Et_2O 95:5, two consecutive purifications) to afford racemic product **3b** (29.6 mg, 0.124 mmol, 62% yield) as colorless oil. The enantiomers of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) were separated by UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/*i*-PrOH for 5 min; isocratic 60:40 CO_2/*i*-PrOH for 2 min, gradient from 60:40 CO_2/*i*-PrOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 346 nm, **3b**: τ = 6.3 min and τ = 6.5 min. The characterization of the title compound was consistent with the data available in the literature (*24*).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.58 (t, *J* = 2.0 Hz, 1H), 7.32 – 7.25 (m, 2H), 7.23 – 7.14 (m, 3H), 7.05 (d, *J* = 7.8 Hz, 2H), 6.96 (d, *J* = 7.9 Hz, 2H), 3.52 – 3.42 (m, 1H), 2.94 (dd, *J* = 13.6, 6.9 Hz, 1H), 2.83 (dd, *J* = 13.6, 8.1 Hz, 1H), 2.77 – 2.70 (m, 2H), 2.30 (s, 3H).

3-Phenyl-4-(*m*-tolyl)butanal (3c)



3c

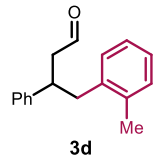
Prepared according to **GP2**, using silane **14c** (36 mg, 0.2 mmol), the racemic amine catalyst **A-2** (9.9 mg, 40 µmol), the photocatalyst Mes-Acr (2.9 mg, 5 µmol, 2.5 mol%) and cinnamaldehyde **1a** (51 µL, 0.4 mmol) in 0.3 M acetonitrile solution of TFA (9.2 µL, 0.12 mmol, 60 mol%). The solution was irradiated for 16h at room temperature. The crude mixture was purified by flash column chromatography (SiO_2, hexane:Et_2O 95:5, two consecutive purifications) to afford racemic product **3c** (18.8 mg, 0.08 mmol, 39% yield) as colorless oil. The enantiomers of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) were separated by UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/*i*-PrOH for 5 min; isocratic 60:40 CO_2/*i*-PrOH for 2 min, gradient from 60:40 CO_2/*i*-PrOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 348 nm, **3c**: τ = 6.3 min and τ = 6.4 min.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.58 (t, *J* = 2.0 Hz, 1H), 7.33 – 7.26 (m, 2H), 7.24 – 7.17 (m, 3H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.01 (ddt, *J* = 7.6, 1.9, 0.9 Hz, 1H), 6.91 (pd, *J* = 1.3, 0.9 Hz, 1H), 6.89 – 6.84 (m, 1H), 3.49 (tt, *J* = 8.3, 6.7 Hz, 1H), 2.95 (dd, *J* = 13.5, 6.7 Hz, 1H), 2.83 (dd, *J* = 13.5, 8.3 Hz, 1H), 2.78 – 2.70 (m, 2H), 2.30 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.84, 143.54, 139.33, 138.05, 130.16, 128.73, 128.33, 127.63, 127.23, 126.85, 126.38, 48.96, 43.45, 42.16, 21.49.

HRMS (APCI): calculated for $[M-H]^+$ $[C_{17}H_{17}O]^+$: 237.1274; found: 237.1269.

3-Phenyl-4-(*o*-tolyl)butanal (3d)



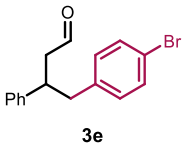
3d

Prepared according to **GP2**, using silane **14d** (40 µL, 0.2 mmol), the racemic amine catalyst **A-2** (9.9 mg, 40 µmol), the photocatalyst Mes-Acr (2.9 mg, 5 µmol, 2.5 mol%) and cinnamaldehyde **1a** (51 µL, 0.4 mmol) in 0.3 M acetonitrile solution of TFA (9.2 µL, 0.12 mmol, 60 mol%). The solution was irradiated for 16h at room temperature. The crude mixture was purified by flash column chromatography (SiO2, hexane:Et_2O 95:5, two consecutive purifications) to afford racemic product **3d** (31.0 mg, 0.13 mmol, 65% yield) as colorless oil. The enantiomers of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) were separated by UPC^2 analysis on a Daicel Chiralpak ID-3 column:

isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/*i*-PrOH for 5 min; isocratic 60:40 CO_2/*i*-PrOH for 2 min, gradient from 60:40 CO_2/*i*-PrOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 348 nm, **3d**: τ = 6.3 min and τ = 6.5 min. The characterization of the title compound was consistent with the data available in the literature.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.58 (t, *J* = 2.0 Hz, 1H), 7.31 – 7.26 (m, 2H), 7.24 – 7.14 (m, 3H), 7.14 – 7.02 (m, 4H), 6.99 – 6.94 (m, 1H), 3.47 (p, *J* = 7.7 Hz, 1H), 2.97 – 2.86 (m, 2H), 2.86 – 2.73 (m, 1H), 2.26 (s, 3H).

4-(4-Bromophenyl)-3-phenylbutanal (3e)

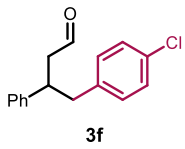


3e

Prepared according to **GP2**, using silane **14e** (40 µL, 0.2 mmol), the racemic amine catalyst **A-2** (9.9 mg, 40 µmol), the photocatalyst Mes-Acr (2.9 mg, 5 µmol, 2.5 mol%) and cinnamaldehyde **1a** (51 µL, 0.4 mmol) in 0.3 M acetonitrile solution of TFA (9.2 µL, 0.12 mmol, 60 mol%). The solution was irradiated for 16h at room temperature. The crude mixture was purified by flash column chromatography (SiO2, two consecutive purifications with hexane:Et_2O 95:5 then toluene) to afford racemic product **3e** (27.0 mg, 0.09 mmol, 44% yield) as white solid. The enantiomers of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) were separated by UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/*i*-PrOH for 5 min; isocratic 60:40 CO_2/*i*-PrOH for 2 min, gradient from 60:40 CO_2/*i*-PrOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 347 nm, **3e**: τ = 7.3 min and τ = 7.6 min. The characterization of the title compound was consistent with the data available in the literature (*24*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (t, *J* = 1.8 Hz, 1H), 7.37 – 7.30 (m, 2H), 7.31 – 7.24 (m, 2H), 7.24 – 7.16 (m, 1H), 7.15 – 7.08 (m, 2H), 6.92 – 6.85 (m, 2H), 3.45 (p, *J* = 7.4 Hz, 1H), 2.88 (dd, *J* = 7.4, 1.4 Hz, 2H), 2.84 – 2.69 (m, 2H).

4-(4-Chlorophenyl)-3-phenylbutanal (3f)

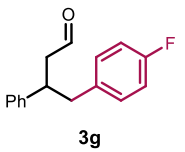


3f

Prepared according to **GP2**, using silane **14f** (40 µL, 0.2 mmol), the racemic amine catalyst **A-2** (9.9 mg, 40 µmol), the photocatalyst Mes-Acr (2.9 mg, 5 µmol, 2.5 mol%) and cinnamaldehyde **1a** (51 µL, 0.4 mmol) in 0.3 M acetonitrile solution of TFA (9.2 µL, 0.12 mmol, 60 mol%). The solution was irradiated for 16h at room temperature. The crude mixture was purified by flash column chromatography (SiO_2, two consecutive purifications with hexane:Et_2O 95:5 then toluene) to afford racemic product **3f** (29.0 mg, 0.11 mmol, 56% yield) as white solid. The enantiomers of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) were separated by UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/*i*-PrOH for 5 min; isocratic 60:40 CO_2/*i*-PrOH for 2 min, gradient from 60:40 CO_2/*i*-PrOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 347 nm, **3f**: τ = 6.8 min and τ = 7.1 min. The characterization of the title compound was consistent with the data available in the literature (*57*).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.63 (t, *J* = 1.8 Hz, 1H), 7.30 – 7.24 (m, 2H), 7.24 – 7.14 (m, 3H), 7.14 – 7.08 (m, 2H), 6.96 – 6.90 (m, 2H), 3.45 (p, *J* = 7.4 Hz, 1H), 2.94 – 2.84 (m, 2H), 2.84 – 2.68 (m, 2H).

4-(4-Fluorophenyl)-3-phenylbutanal (3g)



3g

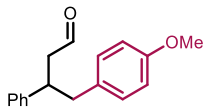
Prepared according to **GP2**, using silane **14g** (36 mg, 0.2 mmol), the racemic amine catalyst **A-2** (9.9 mg, 40 µmol), the photocatalyst Mes-Acr (2.9 mg, 5 µmol, 2.5 mol%) and cinnamaldehyde **1a** (51 µL, 0.4 mmol) in 0.3 M acetonitrile solution of TFA (9.2 µL, 0.12 mmol, 60 mol%). The solution was

irradiated for 16h at room temperature. The crude mixture was purified by flash column chromatography (SiO_2, two consecutive purifications with hexane:Et_2O 95:5 then toluene) to afford racemic product **3g** (28.7 mg, 0.12 mmol, 59% yield) as colorless oil. The enantiomers of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) were separated by UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/*i*-PrOH for 5 min; isocratic 60:40 CO_2/*i*-PrOH for 2 min, gradient from 60:40 CO_2/*i*-PrOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 347 nm, **3g**: τ = 6.2 min and τ = 6.5 min. The characterization of the title compound was consistent with the data available in the literature (*24*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (t, *J* = 1.9 Hz, 1H), 7.32 – 7.23 (m, 2H), 7.23 – 7.17 (m, 1H), 7.16 – 7.08 (m, 2H), 7.01 – 6.93 (m, 2H), 6.93 – 6.85 (m, 2H), 3.44 (p, *J* = 7.4 Hz, 1H), 2.89 (d, *J* = 7.4 Hz, 2H), 2.84 – 2.69 (m, 2H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -116.52.

4-(4-Methoxyphenyl)-3-phenylbutanal (3h)

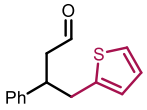


3h

Prepared according to **GP2**, using silane **14h** (39 mg, 0.2 mmol), the racemic amine catalyst **A-2** (9.9 mg, 40 µmol), the photocatalyst Mes-Acr (2.9 mg, 5 µmol, 2.5 mol%) and cinnamaldehyde **1a** (51 µL, 0.4 mmol) in 0.3 M acetonitrile solution of TFA (9.2 µL, 0.12 mmol, 60 mol%). The solution was irradiated for 16h at room temperature. The crude mixture was purified by flash column chromatography (SiO_2, hexane:Et_2O 95:5, two consecutive purifications) afford racemic product **3h** (25.7 mg, 0.10 mmol, 50% yield) as colorless oil. The enantiomers of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) were separated by UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/*i*-PrOH for 5 min; isocratic 60:40 CO_2/*i*-PrOH for 2 min, gradient from 60:40 CO_2/*i*-PrOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 349 nm, **3h**: τ = 7.0 min and τ = 7.2 min. The characterization of the title compound was consistent with the data available in the literature (*24*).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.59 (t, *J* = 2.0 Hz, 1H), 7.29 (dd, *J* = 8.1, 6.8 Hz, 2H), 7.24 – 7.18 (m, 1H), 7.18 – 7.14 (m, 2H), 7.00 – 6.95 (m, 2H), 6.80 – 6.77 (m, 2H), 3.77 (s, 3H), 3.46 (p, *J* = 7.4 Hz, 1H), 2.92 (dd, *J* = 13.7, 7.1 Hz, 1H), 2.83 (dd, *J* = 13.7, 7.8 Hz, 1H), 2.75 (dt, *J* = 6.8, 2.1 Hz, 2H).

3-Phenyl-4-(thiophen-2-yl)butanal (3i)

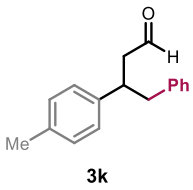


3i

Prepared according to **GP2**, using silane **14i** (34 mg, 0.2 mmol), the racemic amine catalyst **A-2** (9.9 mg, 40 µmol), the photocatalyst Mes-Acr (2.9 mg, 5 µmol, 2.5 mol%) and cinnamaldehyde **1a** (51 µL, 0.4 mmol) in 0.3 M acetonitrile solution of TFA (9.2 µL, 0.12 mmol, 60 mol%). The solution was irradiated for 16h at room temperature. The crude mixture was purified by flash column chromatography (SiO_2, hexane:Et_2O 95:5, two consecutive purifications) to afford racemic product **3i** (26.4 mg, 0.11 mmol, 57% yield) as colorless oil. The enantiomers of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) were separated by UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/*i*-PrOH for 5 min; isocratic 60:40 CO_2/*i*-PrOH for 2 min, gradient from 60:40 CO_2/*i*-PrOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 348 nm, **3i**: τ = 6.7 min and τ = 6.9 min.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.62 (t, *J* = 1.9 Hz, 1H), 7.31 (ddt, *J* = 7.2, 6.6, 0.9 Hz, 2H), 7.25 – 7.18 (m, 3H), 7.10 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.87 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.69 (dq, *J* = 3.4, 0.9 Hz, 1H), 3.52 (p, *J* = 7.4 Hz, 1H), 3.21 – 3.10 (m, 2H), 2.82 – 2.78 (m, 2H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 201.30, 142.94, 141.73, 128.83, 127.65, 127.09, 126.88, 125.99, 124.01, 49.18, 42.41, 37.15.
HRMS (APCI): calculated for $[M+H]^+$ $[C_{14}H_{15}OS]^+$: 231.0838; found: 231.0843.

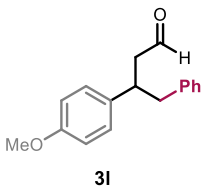
4-Phenyl-3-(p-tolyl)butanal (3k)



3k

Prepared according to **GP2**, using benzyltrimethylsilane **14a** (38 µL, 0.2 mmol), the racemic amine catalyst **A-2** (9.9 mg, 40 µmol), the photocatalyst Mes-Acr (2.9 mg, 5 µmol, 2.5 mol%) and enal **1b** (58 mg, 0.4 mmol) in 0.3 M acetonitrile solution of TFA (9.2 µL, 0.12 mmol, 60 mol%). The solution was irradiated for 16h at room temperature. The crude mixture was purified by flash column chromatography (SiO_2, hexane:Et_2O 95:5, two consecutive purifications) to afford racemic product **3k** (23.7 mg, 0.10 mmol, 50% yield) as colorless oil. The enantiomers of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) were separated by UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/*i*-PrOH for 5 min; isocratic 60:40 CO_2/*i*-PrOH for 2 min, gradient from 60:40 CO_2/*i*-PrOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 347 nm, **3k**: τ = 6.3 min and τ = 6.5 min. The characterization of the title compound was consistent with the data available in the literature (*24*).
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.58 (t, *J* = 2.0 Hz, 1H), 7.29 – 7.22 (m, 2H), 7.22 – 7.16 (m, 1H), 7.14 – 6.96 (m, 6H), 3.47 (tt, *J* = 8.1, 6.7 Hz, 1H), 2.96 (dd, *J* = 13.5, 7.0 Hz, 1H), 2.87 (dd, *J* = 13.5, 8.0 Hz, 1H), 2.79 – 2.66 (m, 2H), 2.32 (s, 3H).

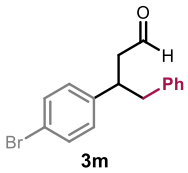
3-(4-Methoxyphenyl)-4-phenylbutanal (3l)



3l

Prepared according to **GP2**, using benzyltrimethylsilane **14a** (38 µL, 0.2 mmol), the racemic amine catalyst **A-2** (9.9 mg, 40 µmol), the photocatalyst Mes-Acr (2.9 mg, 5 µmol, 2.5 mol%) and enal **1c** (65 mg, 0.4 mmol) in 0.3 M acetonitrile solution of TFA (9.2 µL, 0.12 mmol, 60 mol%). The solution was irradiated for 16h at room temperature. The crude mixture was purified by flash column chromatography (SiO_2, hexane:Et_2O 95:5, two consecutive purifications) to afford racemic product **3l** (24.6 mg, 0.10 mmol, 48% yield) as colorless oil. The enantiomers of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) were separated by UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/*i*-PrOH for 5 min; isocratic 60:40 CO_2/*i*-PrOH for 2 min, gradient from 60:40 CO_2/*i*-PrOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 347 nm, **3l**: τ = 6.8 min and τ = 7.0 min.
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.58 (t, *J* = 2.0 Hz, 1H), 7.33 – 7.20 (m, 2H), 7.21 – 7.14 (m, 1H), 7.12 – 7.00 (m, 4H), 6.86 – 6.76 (m, 2H), 3.78 (s, 3H), 3.45 (p, *J* = 7.4 Hz, 1H), 2.93 (dd, *J* = 13.5, 7.2 Hz, 1H), 2.86 (dd, *J* = 13.5, 7.8 Hz, 1H), 2.75 – 2.67 (m, 2H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 201.94, 158.43, 139.51, 135.35, 129.37, 128.58, 128.43, 126.42, 114.10, 55.35, 49.27, 43.65, 41.39.
HRMS (ESI): calculated for $[M+MeOH+Na]^+$ $[C_{18}H_{22}NaO_3]^+$: 309.1461; found: 309.1463.

3-(4-Bromophenyl)-4-phenylbutanal (3m)



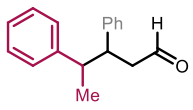
3m

Prepared according to **GP2**, using benzyltrimethylsilane **14a** (38 µL, 0.2 mmol), the racemic amine catalyst **A-2** (9.9 mg, 40 µmol), the photocatalyst Mes-Acr (2.9 mg, 5 µmol, 2.5 mol%) and enal **1d** (84 mg, 0.4 mmol) in 0.3 M acetonitrile solution of TFA (9.2 µL, 0.12 mmol, 60 mol%). The solution was irradiated for 16h at room temperature. The crude mixture was purified by flash column chromatography (SiO_2, two consecutive purifications: hexane:Et_2O 95:5 then toluene) to afford racemic product **3m** (43.3 mg, 0.14 mmol, 71% yield) as colorless crystals. The enantiomers of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) were separated by UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/MeOH for 13 min; isocratic 60:40 CO_2/MeOH for 2 min, gradient from 60:40 CO_2/MeOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 350 nm: ***3m***: τ = 13.2 min and τ = 13.5 min. The characterization of the title compound was consistent with the data available in the literature (*24*).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.60 (t, *J* = 1.7 Hz, 1H), 7.42 – 7.37 (m, 2H), 7.26 – 7.21 (m, 2H), 7.21 – 7.16 (m, 1H), 7.03 (td, *J* = 6.2, 1.8 Hz, 4H), 3.47 (p, *J* = 7.4 Hz, 1H), 2.89 (d, *J* = 7.5 Hz, 2H), 2.75 (dd, *J* = 7.3, 1.7 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.04, 142.36, 138.94, 131.76, 129.41, 129.29, 128.52, 126.59, 120.57, 49.02, 43.17, 41.44.

3,4-Diphenylpentanal (5a)

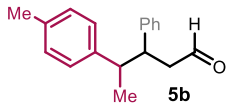


5a

Prepared according to **GP2**, using silane **15a** (41 µL, 0.2 mmol), the racemic amine catalyst **A-2** (9.9 mg, 40 µmol), the photocatalyst Mes-Acr (2.9 mg, 5 µmol, 2.5 mol%) and cinnamaldehyde **1a** (51 µL, 0.4 mmol) in 0.3 M acetonitrile solution of TFA (9.2 µL, 0.12 mmol, 60 mol%). The solution was irradiated for 16h at room temperature. The crude mixture was purified by flash column chromatography (SiO_2, hexane:Et_2O 95:5, two consecutive purifications) to afford the racemic product as an inseparable mixture of two diastereomers *syn*-**5a** and *anti*-**5a** (27.6 mg, 0.12 mmol, 58% yield, 1.2:1 d.r.) as colorless oil. The enantiomers of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) were separated by UPC^2 analysis on a Daicel Chiralpak IE-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/*i*-PrOH for 15 min; isocratic60:40 CO_2/ *i*-PrOH for 8 min, gradient from 60:40 CO_2/*i*-PrOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 345 nm: *syn*-**5a**: τ = 19.3 min and τ = 19.5 min; *anti*-**5a**: τ = 21.2 min and τ = 21.6 min. The characterization of the title compound was consistent with the data available in the literature (24).

^{1}H NMR (400 MHz, $CDCl_3$, *mixture of diastereoisomers*) δ 9.57 (t, *J* = 2.1 Hz, 1H), 9.35 (dd, *J* = 2.5, 1.6 Hz, 1H), 7.37 – 7.29 (m, 4H), 7.26 – 7.09 (m, 12H), 6.98 (ddd, *J* = 8.0, 3.0, 1.5 Hz, 4H), 3.46 (q, *J* = 7.3 Hz, 1H), 3.30 (td, *J* = 10.2, 4.6 Hz, 1H), 3.07 (p, *J* = 7.0 Hz, 1H), 2.89 (dt, *J* = 11.1, 6.9 Hz, 1H), 2.83 – 2.77 (m, 2H), 2.62 (ddd, *J* = 16.8, 10.0, 2.5 Hz, 1H), 2.47 (ddd, *J* = 16.8, 4.6, 1.6 Hz, 1H), 1.29 (d, *J* = 7.1 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H).

3-Phenyl-4-(*p*-tolyl)pentanal (5b)



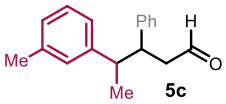
5b

Prepared according to **GP2**, using silane **15b** (38 mg, 0.2 mmol), the racemic amine catalyst **A-2** (9.9 mg, 40 µmol), the photocatalyst Mes-Acr (2.9 mg, 5 µmol, 2.5 mol%) and cinnamaldehyde **1a** (51 µL, 0.4 mmol) in 0.3 M acetonitrile solution of TFA (9.2 µL, 0.12 mmol, 60 mol%). The solution was irradiated for 16h at room temperature. The crude mixture was purified by flash column chromatography (SiO_2, two consecutive purifications with hexane:Et_2O 95:5) to afford

racemic product as an inseparable mixture of two diastereomers *syn*-**5b** and *anti*-**5b** (40.0 mg, 0.16 mmol, 79% yield, 1.1:1 d.r.) as yellowish oil. The enantiomers of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) were separated by UPC^2 analysis on a Daicel Chiralpak IA-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/EtOH for 11 min; isocratic 60:40 CO_2/EtOH for 6 min, gradient from 60:40 CO_2/EtOH to 100% CO_2 for 1 min, flow rate 1.0 mL/min, λ = 352 nm: *syn*-**5b**: τ = 16.1 min and τ = 16.5 min; *anti*-**5b**: τ = 13.8 min and τ = 14.3 min. The characterization of the title compound was consistent with the data available in the literature (*32*).

^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereoisomers) δ 9.58 (t, *J* = 2.1 Hz, 1H), 9.37 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.35 (dd, *J* = 8.1, 6.7 Hz, 2H), 7.28 – 7.20 (m, 6H), 7.16 (d, *J* = 1.5 Hz, 4H), 7.05 – 7.00 (m, 4H), 6.91 (d, *J* = 8.0 Hz, 2H), 3.48 (q, *J* = 7.2 Hz, 1H), 3.29 (td, *J* = 10.2, 4.7 Hz, 1H), 3.07 (p, *J* = 6.9 Hz, 1H), 2.88 (dq, *J* = 10.5, 6.9 Hz, 1H), 2.83 – 2.78 (m, 2H), 2.63 (ddd, *J* = 16.7, 10.0, 2.6 Hz, 1H), 2.50 (ddd, *J* = 16.7, 4.7, 1.6 Hz, 1H), 2.37 (s, 3H), 2.30 (s, 3H), 1.27 (d, *J* = 7.1 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H).

3-Phenyl-4-(*m*-tolyl)pentanal (5c)



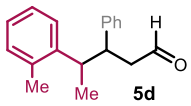
Prepared according to **GP2**, using silane **15c** (38 mg, 0.2 mmol), the racemic amine catalyst **A-2** (9.9 mg, 40 µmol), the photocatalyst Mes-Acr (2.9 mg, 5 µmol, 2.5 mol%) and cinnamaldehyde **1a** (51 µL, 0.4 mmol) in 0.3 M acetonitrile solution of TFA (9.2 µL, 0.12 mmol, 60 mol%). The solution was irradiated for 16h at room temperature. The crude mixture was purified by flash column chromatography (SiO_2, hexane:Et_2O 95:5, two consecutive purifications) to afford the racemic product as an inseparable mixture of two diastereomers *syn*-**5c** and *anti*-**5c** (24.3 mg, 0.10 mmol, 51% yield, 1:1.1 d.r.) as colorless oil. The enantiomers of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) were separated by UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/ EtOH for 13 min; isocratic 60:40 CO_2/EtOH for 2 min, gradient from 60:40 CO_2/EtOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 347 nm: *syn*-**5c**: τ = 10.0 min and τ = 10.4 min; *anti*-**5c**: τ = 10.7 min and τ = 11.3 min.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereoisomers) δ 9.57 (t, *J* = 2.1 Hz, 1H), 9.37 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.35 (td, *J* = 7.4, 1.4 Hz, 2H), 7.29 – 7.20 (m, 6H), 7.19 – 7.14 (m, 1H), 7.14 – 7.05 (m, 4H), 7.05 – 6.96 (m, 3H), 6.85 – 6.79 (m, 2H), 3.49 (dt, *J* = 9.0, 6.4 Hz, 1H), 3.31 (td, *J* = 10.2, 4.5 Hz, 1H), 3.06 (p, *J* = 7.0 Hz, 1H), 2.92 – 2.84 (m, 1H), 2.84 – 2.74 (m, 2H), 2.63 (ddd, *J* = 16.8, 10.2, 2.6 Hz, 1H), 2.49 (ddd, *J* = 16.8, 4.5, 1.6 Hz, 1H), 2.39 (s, 3H), 2.29 (s, 3H), 1.28 (d, *J* = 7.1 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereoisomers) δ 202.22, 201.80, 145.22, 143.80, 142.86, 141.64, 138.38, 137.56, 129.01, 128.74, 128.69, 128.66, 128.43, 128.23, 128.14, 127.96, 127.57, 127.14, 126.89, 126.64, 125.20, 124.71, 49.17, 47.62, 46.55, 46.10, 45.89, 44.98, 21.62, 21.52, 20.70, 17.75.

HRMS (ESI): Calculated for $[M+MeOH+Na]^+$ $[C_{19}H_{24}NaO_2]^+$: 307.1669, found: 307.1669.

3-Phenyl-4-(*o*-tolyl)pentanal (5d)



Prepared according to **GP2**, using silane **15d** (38 mg, 0.2 mmol), the racemic amine catalyst **A-2** (9.9 mg, 40 µmol), the photocatalyst Mes-Acr (2.9 mg, 5 µmol, 2.5 mol%) and cinnamaldehyde **1a** (51 µL, 0.4 mmol) in 0.3 M acetonitrile solution of TFA (9.2 µL, 0.12 mmol, 60 mol%). The solution was irradiated for 16h at room temperature. The crude mixture was purified by flash column chromatography (SiO_2, hexane:Et_2O 95:5, two consecutive purifications) to afford the racemic product as an inseparable mixture of two diastereomers *syn*-**5d** and *anti*-**5d** (37.6 mg, 0.16 mmol, 79% yield, 1:1.1 d.r.) as colorless oil. The enantiomers of the corresponding 2,4-

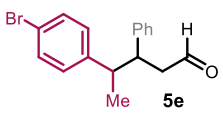
dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) were separated by UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/ MeOH for 13 min; isocratic 60:40 CO_2/MeOH for 2 min, gradient from 60:40 CO_2/MeOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 350 nm: *syn*-**5d**: τ = 9.6 min and τ = 10.0 min; *anti*-**5d**: τ = 10.4 min and τ = 11.2 min.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereoisomers) δ 9.57 (t, *J* = 2.1 Hz, 1H), 9.37 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.35 (td, *J* = 7.4, 1.4 Hz, 2H), 7.31 – 7.20 (m, 6H), 7.19 – 7.14 (m, 1H), 7.14 – 7.04 (m, 4H), 7.04 – 6.97 (m, 3H), 6.86 – 6.79 (m, 2H), 3.49 (dt, *J* = 9.0, 6.4 Hz, 1H), 3.31 (td, *J* = 10.3, 4.5 Hz, 1H), 3.06 (p, *J* = 7.0 Hz, 1H), 2.92 – 2.84 (m, 1H), 2.84 – 2.74 (m, 2H), 2.63 (ddd, *J* = 16.8, 10.1, 2.6 Hz, 1H), 2.49 (ddd, *J* = 16.8, 4.5, 1.6 Hz, 1H), 2.39 (s, 3H), 2.29 (s, 3H), 1.28 (d, *J* = 7.1 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereoisomers) δ 202.22, 201.80, 145.22, 143.80, 142.86, 141.64, 138.38, 137.56, 129.01, 128.74, 128.69, 128.66, 128.43, 128.23, 128.14, 127.96, 127.57, 127.14, 126.89, 126.64, 125.20, 124.71, 49.17, 47.62, 46.55, 46.10, 45.89, 44.98, 21.62, 21.52, 20.70, 17.75.

HRMS (ESI): Calculated for $[M+MeOH+Na]^+$ $[C_{19}H_{24}NaO_2]^+$: 307.1669, found: 307.1682.

4-(4-Bromophenyl)-3-phenylpentanal (5e)



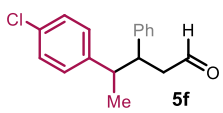
Prepared according to **GP2**, using silane **15e** (51 mg, 0.2 mmol), the racemic amine catalyst **A-2** (9.9 mg, 40 µmol), the photocatalyst Mes-Acr (2.9 mg, 5 µmol, 2.5 mol%) and cinnamaldehyde **1a** (51 µL, 0.4 mmol) in 0.3 M acetonitrile solution of TFA (9.2 µL, 0.12 mmol, 60 mol%). The solution was irradiated for 16 h at room temperature. The crude mixture was purified by flash column chromatography (SiO_2, hexane:Et_2O 95:5, two consecutive purifications) to afford the racemic product as an inseparable mixture of two diastereomers *syn*-**5e** and *anti*-**5e** (29.4 mg, 0.09 mmol, 46% yield, 1:1.1 d.r.) as colorless crystals. The enantiomers of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) were separated by UPC^2 analysis on a Daicel Chiralpak IB-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 85:15 CO_2/*i*-PrOH for 37 min; isocratic 85:15 CO_2/ *i*-PrOH for 26 min, gradient from 85:15 CO_2/ *i*-PrOH to 100% CO_2 for 1 min, flow rate 1.0 mL/min, λ = 344 nm: *syn*-**5e**: τ = 50.8 min and τ = 54.9 min; *anti*-**5e**: τ = 58.8 min and τ = 60.0 min.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereoisomers) δ 9.59 (t, *J* = 2.0 Hz, 1H), 9.39 (dd, *J* = 2.4, 1.4 Hz, 1H), 7.49 – 7.42 (m, 2H), 7.36 – 7.27 (m, 4H), 7.27 – 7.17 (m, 5H), 7.17 – 7.12 (m, 1H), 7.12 – 7.07 (m, 2H), 6.97 – 6.93 (m, 2H), 6.85 – 6.81 (m, 2H), 3.41 (q, *J* = 7.4 Hz, 1H), 3.28 (td, *J* = 10.1, 4.5 Hz, 1H), 3.02 (p, *J* = 7.1 Hz, 1H), 2.89 (dq, *J* = 10.1, 6.9 Hz, 1H), 2.80 (dd, *J* = 7.5, 2.1 Hz, 2H), 2.64 (ddd, *J* = 16.8, 10.1, 2.4 Hz, 1H), 2.46 (ddd, *J* = 16.9, 4.5, 1.5 Hz, 1H), 1.27 (d, *J* = 7.1 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereoisomers) δ 201.77, 201.37, 144.26, 142.98, 142.22, 141.21, 131.88, 131.16, 129.89, 129.45, 128.80, 128.58, 128.32, 128.24, 127.07, 126.84, 120.48, 120.14, 48.80, 47.25, 46.64, 46.45, 45.49, 44.68, 20.38, 18.65.

HRMS (ESI): Calculated for $[M+Na]^+$ $[C_{17}H_{17}BrNaO]^+$: 339.0355, found: 339.0343.

4-(4-Chlorophenyl)-3-phenylpentanal (5f)



Prepared according to **GP2**, using silane **15f** (43 mg, 0.2 mmol), the racemic amine catalyst **A-2** (9.9 mg, 40 µmol), the photocatalyst Mes-Acr (2.9 mg, 5 µmol, 2.5 mol%) and cinnamaldehyde **1a** (51 µL, 0.4 mmol) in 0.3 M acetonitrile solution of TFA (9.2 µL, 0.12 mmol, 60 mol%). The solution was irradiated for 16h at room temperature. The crude mixture was purified by flash column chromatography (SiO_2 two consecutive purifications: hexane:Et_2O 95:5 then toluene) to afford the racemic product as an inseparable mixture of two diastereomers *syn*-**5f** and *anti*-**5f** (24.3 mg,

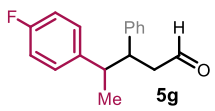
0.09 mmol, 45% yield, 1:1.1 d.r.) as white solid The enantiomers of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) were separated by UPC^2 analysis on a Daicel Chiralpak IE-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/ EtOH for 21 min; isocratic 60:40 CO_2/EtOH for 6 min, gradient from 60:40 CO_2/EtOH to 100% CO_2 for 1 min, flow rate: 1.0 mL/min, λ = 350 nm: *syn*-**5f**: τ = 22.1 min and τ = 22.7 min; *anti*-**5f**: τ = 23.2 min and τ = 23.5 min.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereoisomers) δ 9.59 (t, *J* = 2.0 Hz, 1H), 9.39 (dd, *J* = 2.4, 1.5 Hz, 1H), 7.37 – 7.11 (m, 14H), 6.97 – 6.93 (m, 2H), 6.91 – 6.85 (m, 2H), 3.41 (q, *J* = 7.4 Hz, 1H), 3.27 (td, *J* = 10.1, 4.5 Hz, 1H), 3.03 (p, *J* = 7.1 Hz, 1H), 2.90 (dq, *J* = 10.1, 6.9 Hz, 1H), 2.80 (dd, *J* = 7.5, 2.0 Hz, 2H), 2.64 (ddd, *J* = 16.9, 10.1, 2.4 Hz, 1H), 2.46 (ddd, *J* = 16.9, 4.5, 1.5 Hz, 1H), 1.28 (d, *J* = 7.0 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereoisomers) δ 201.81, 201.40, 143.72, 142.45, 142.26, 141.24, 132.46, 132.05, 129.48, 129.06, 128.94, 128.81, 128.60, 128.32, 128.25, 128.22, 127.07, 126.83, 48.83, 47.35, 46.66, 46.54, 45.44, 44.64, 20.44, 18.69.

HRMS (ESI): Calculated for $[M+MeOH+Na]^+$ $[C_{18}H_{21}ClNaO_2]^+$: 327.1122, found: 327.1132.

4-(4-Fluorophenyl)-3-phenylpentanal (5g)



Prepared according to **GP2**, using silane **15g** (39 mg, 0.2 mmol), the racemic amine catalyst **A-2** (9.9 mg, 40 µmol), the photocatalyst Mes-Acr (2.9 mg, 5 µmol, 2.5 mol%) and cinnamaldehyde **1a** (51 µL, 0.4 mmol) in 0.3 M acetonitrile solution of TFA (9.2 µL, 0.12 mmol, 60 mol%). The solution was irradiated for 16h at room temperature. The crude mixture was purified by flash column chromatography (SiO_2 two consecutive purifications: hexane:Et_2O 95:5 then toluene) to afford the racemic product as an inseparable mixture of two diastereomers *syn*-**5g** and *anti*-**5g** (34.9 mg, 0.14 mmol, 68% yield, 1:1.2 d.r.) as colorless oil. The enantiomers of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) were separated by UPC^2 analysis on a Daicel Chiralpak IE-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 70:30 CO_2/ EtOH for 9 min; isocratic 70:30 CO_2/EtOH for 4 min, gradient from 70:30 CO_2/EtOH to 100% CO_2 for 1 min, flow rate: 2.0 mL/min, λ = 347 nm: *syn*-**5g**: τ = 10.7 min and τ = 10.7 min; *anti*-**5g**: τ = 11.3 min and τ = 11.5 min.

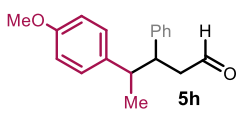
^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereoisomers) δ 9.59 (t, *J* = 2.0 Hz, 1H), 9.38 (dd, *J* = 2.4, 1.6 Hz, 1H), 7.36 – 7.29 (m, 2H), 7.27 – 7.10 (m, 8H), 7.07 – 6.98 (m, 2H), 6.96 – 6.83 (m, 6H), 3.41 (q, *J* = 7.4 Hz, 1H), 3.27 (td, *J* = 10.0, 4.6 Hz, 1H), 3.04 (p, *J* = 7.1 Hz, 1H), 2.91 (dq, *J* = 10.1, 6.9 Hz, 1H), 2.85 – 2.77 (m, 2H), 2.63 (ddd, *J* = 16.8, 10.0, 2.4 Hz, 1H), 2.47 (ddd, *J* = 16.8, 4.7, 1.6 Hz, 1H), 1.28 (d, *J* = 7.1 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereoisomers) δ 201.91, 201.48, 162.71, 162.43, 160.76, 160.49, 142.44, 141.36, 140.87, 140.85, 139.59, 139.56, 129.52, 129.46, 129.10, 129.04, 128.78, 128.62, 128.26, 128.24, 115.66, 115.49, 114.92, 114.76, 48.89, 47.60, 46.74, 46.61, 45.31, 44.48, 20.58, 18.75.

^{19}F NMR (471 MHz, $CDCl_3$, mixture of diastereoisomers) δ -116.22, -116.83.

HRMS (ESI): Calculated for $[M+MeOH+Na]^+$ $[C_{18}H_{21}FNaO_2]^+$: 311.1418, found: 311.1422.

4-(4-Methoxyphenyl)-3-phenylpentanal (5h)



Prepared according to **GP2**, using silane **15h** (42 mg, 0.2 mmol), the racemic amine catalyst **A-2** (9.9 mg, 40 µmol), the photocatalyst Mes-Acr (2.9 mg, 5 µmol, 2.5 mol%) and cinnamaldehyde **1a** (51 µL, 0.4 mmol) in 0.3 M acetonitrile solution of TFA (9.2 µL, 0.12 mmol, 60 mol%). The solution was irradiated for 16h at room temperature. The crude mixture was purified by flash column chromatography (SiO_2, hexane:Et_2O 95:5, two consecutive purifications) to afford the racemic product as an inseparable mixture of two diastereomers *syn*-**5h** and *anti*-**5h** (18.5 mg,

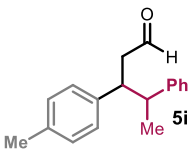
0.07 mmol, 35% yield, 1:1.1 d.r.) as colorless crystals. The enantiomers of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) were separated by UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 70:30 CO_2/ EtOH for 21 min; isocratic 70:30 CO_2/EtOH for 6 min, gradient from 70:30 CO_2/EtOH to 100% CO_2 for 2 min, flow rate 1.0 mL/min, λ = 346 nm: *syn*-**5h**: τ = 20.0 min and τ = 20.6 min; *anti*-**5h**: τ = 21.1 min and τ = 22.1 min.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereoisomers) δ 9.57 (t, *J* = 2.1 Hz, 1H), 9.35 (dd, *J* = 2.5, 1.6 Hz, 1H), 7.38 – 7.28 (m, 2H), 7.25 – 7.17 (m, 6H), 7.17 – 7.12 (m, 3H), 7.01 – 6.94 (m, 2H), 6.92 – 6.84 (m, 3H), 6.76 – 6.72 (m, 2H), 3.81 (s, 3H), 3.76 (s, 3H), 3.43 (q, *J* = 7.3 Hz, 1H), 3.25 (td, *J* = 10.1, 4.7 Hz, 1H), 3.03 (p, *J* = 7.0 Hz, 1H), 2.86 (dq, *J* = 10.3, 6.9 Hz, 1H), 2.78 (dd, *J* = 7.4, 2.0 Hz, 2H), 2.60 (ddd, *J* = 16.7, 9.9, 2.5 Hz, 1H), 2.49 (ddd, *J* = 16.7, 4.7, 1.6 Hz, 1H), 1.25 (d, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereoisomers) δ 202.29, 201.85, 158.47, 158.12, 142.90, 141.56, 137.24, 135.84, 129.13, 128.75, 128.74, 128.62, 128.24, 128.19, 126.90, 126.66, 114.17, 113.47, 55.40, 55.31, 49.15, 47.89, 46.73, 46.27, 45.31, 44.19, 20.75, 18.27.

HRMS (ESI): Calculated for $[M+Na]^+$ $[C_{18}H_{20}NaO_2]^+$: 291.1356, found: 291.1355.

4-Phenyl-3-(*p*-tolyl)pentanal (5i)



5i

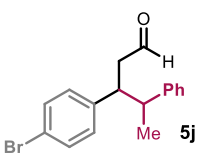
Prepared according to **GP2**, using silane **15a** (41 µL, 0.2 mmol), the racemic amine catalyst **A-2** (9.9 mg, 40 µmol), the photocatalyst Mes-Acr (2.9 mg, 5 µmol, 2.5 mol%) and enal **1b** (58 mg, 0.4 mmol) in 0.3 M acetonitrile solution of TFA (9.2 µL, 0.12 mmol, 60 mol%). The solution was irradiated for 16h at room temperature. The crude mixture was purified by flash column chromatography (SiO_2, hexane:Et_2O 95:5, two consecutive purifications) to afford the racemic product as an inseparable mixture of two diastereomers *syn*-**5i** and *anti*-**5i** (27.2 mg, 0.11 mmol, 54% yield, 1:1.1 d.r.) as colorless oil. The enantiomers of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) were separated by UPC^2 analysis on a Daicel Chiralpak IE-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/MeOH for 14 min; isocratic 60:40 CO_2/EtOH for 4 min, gradient from 60:40 CO_2/EtOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 353 nm: *syn*-**5i**: τ = 13.5 min and τ = 13.7 min; *anti*-**5i**: τ = 14.1 min and τ = 14.4 min.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereoisomers) δ 9.55 (t, *J* = 2.2 Hz, 1H), 9.35 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.36 – 7.30 (m, 2H), 7.27 – 7.18 (m, 6H), 7.18 – 7.13 (m, 4H), 7.03 – 6.98 (m, 4H), 6.90 – 6.85 (m, 2H), 3.44 (dt, *J* = 8.6, 6.7 Hz, 1H), 3.27 (td, *J* = 10.3, 4.6 Hz, 1H), 3.06 (p, *J* = 7.0 Hz, 1H), 2.87 (dq, *J* = 10.5, 6.9 Hz, 1H), 2.82 – 2.71 (m, 2H), 2.59 (ddd, *J* = 16.7, 10.1, 2.6 Hz, 1H), 2.44 (ddd, *J* = 16.7, 4.6, 1.6 Hz, 1H), 2.34 (s, 3H), 2.28 (s, 3H), 1.27 (d, *J* = 7.1 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereoisomers) δ 202.40, 201.95, 145.40, 144.01, 139.62, 138.42, 136.46, 136.17, 129.47, 128.92, 128.82, 128.52, 128.23, 128.11, 128.09, 127.71, 126.80, 126.39, 49.18, 47.29, 46.23, 46.19, 46.12, 45.08, 21.18, 21.12, 20.67, 17.94.

HRMS (ESI): Calculated for $[M+Na]^+$ $[C_{18}H_{20}NaO]^+$: 275.1406, found: 275.1395.

3-(4-Bromophenyl)-4-phenylpentanal (5j)



5j

Prepared according to **GP2**, using silane **15a** (41 µL, 0.2 mmol), the racemic amine catalyst **A-2** (9.9 mg, 40 µmol), the photocatalyst Mes-Acr (2.9 mg, 5 µmol, 2.5 mol%) and enal **1d** (84 mg, 0.4 mmol) in 0.3 M acetonitrile solution of TFA (9.2 µL, 0.12 mmol, 60 mol%). The solution was irradiated for 16h at room temperature. The crude mixture was purified by flash column chromatography (SiO_2 two consecutive purifications: hexane:Et_2O 95:5 then toluene) to afford the racemic product as an inseparable mixture of two diastereomers *syn*-**5j** and *anti*-**5j** (44.8 mg,

0.14 mmol, 71% yield, 1:1.1 d.r.) as colorless oil. The enantiomers of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) were separated by UPC^2 analysis on a Daicel Chiralpak IE-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 70:30 CO_2/ EtOH for 5 min; isocratic 70:30 CO_2/EtOH for 10 min, gradient from 70:30 CO_2/EtOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 348 nm: *syn*-**5j**: τ = 10.7 min and τ = 11.2 min; *anti*-**5j**: τ = 12.0 min and τ = 12.3 min.

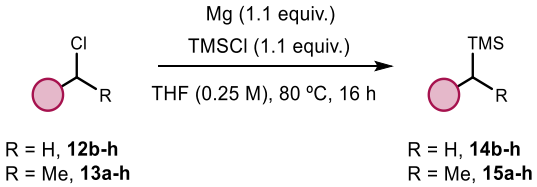
^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereoisomers) δ 9.58 (dd, *J* = 2.3, 1.5 Hz, 1H), 9.36 (dd, *J* = 2.3, 1.3 Hz, 1H), 7.48 – 7.43 (m, 2H), 7.36 – 7.27 (m, 4H), 7.25 – 7.08 (m, 8H), 6.98 – 6.93 (m, 2H), 6.85 – 6.79 (m, 2H), 3.43 (dt, *J* = 9.2, 6.4 Hz, 1H), 3.29 (td, *J* = 10.1, 4.6 Hz, 1H), 3.02 (p, *J* = 7.1 Hz, 1H), 2.91 – 2.82 (m, 1H), 2.82 – 2.70 (m, 2H), 2.60 (ddd, *J* = 17.1, 9.9, 2.3 Hz, 1H), 2.48 (ddd, *J* = 17.1, 4.6, 1.4 Hz, 1H), 1.28 (d, *J* = 7.1 Hz, 3H), 1.04 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, mixture of diastereoisomers) δ 201.50, 201.09, 144.84, 143.48, 141.87, 140.71, 131.87, 131.30, 130.36, 130.01, 128.91, 128.26, 128.15, 127.68, 127.00, 126.62, 120.69, 120.52, 48.99, 46.89, 46.56, 46.03, 45.88, 44.98, 20.49, 18.49.

HRMS (ESI): Calculated for $[M+MeOH+Na]^+$ $[C_{18}H_{21}NaO_2]^+$: 371.0617, found: 371.0607.

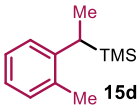
H.2 Synthesis and Characterization of Silanes

GP3 – General Procedure for the Synthesis of Silanes 14 and 15



The general method for the synthesis of silanes **14** and **15** was adapted from a reported procedure (*47*). A round-bottom flask was charged with magnesium tunings (1.1 equiv.), anhydrous THF, and trimethylsilyl chloride (1.1 equiv.). To the resulting suspension, the corresponding benzyl halide **12** or **13** (1 equiv.) in dry THF (0.25 M) was slowly added. The mixture was heated under reflux for 16 h, cooled to room temperature and quenched with saturated aqueous NH_4Cl solution. The solution was extracted with hexane (3 x 25 mL). The combined organic phase was washed with water (1 x 25 mL) and brine (1 x 25mL) and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the crude product was purified by flash column chromatography (SiO_2, hexane) to yield silane **14** or **15**.

Trimethyl (1-(*o*-tolyl)ethyl) silane (15d)

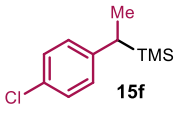


Prepared according to **GP3**, using magnesium tunings (134 mg, 5.5 mmol, 1.1 equiv.), TMSCl (696 µL, 5.5 mmol, 1.1 equiv.) and 1-(1-chloroethyl)-2-methylbenzene **13d** (773 mg, 5.0 mmol, 1.0 equiv.) in dry THF (20 mL). The crude mixture was purified by flash column chromatography (SiO_2, hexane) to afford silane **15d** (632 mg, 3.3 mmol, 66% yield, 90% purity) as a colorless liquid, containing 10% 1-methyl-2-ethylbenzene as inseparable side product.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 – 7.09 (m, 2H), 7.06 (dd, *J* = 7.8, 1.5 Hz, 1H), 6.99 (td, *J* = 7.3, 1.5 Hz, 1H), 2.41 (q, *J* = 7.4 Hz, 1H), 2.26 (s, 3H), 1.35 (d, *J* = 7.4 Hz, 3H), -0.04 (s, 10H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.81, 134.72, 130.14, 126.28, 125.95, 124.08, 24.28, 20.62, 15.84, -2.82.

(1-(4-Chlorophenyl)ethyl)trimethylsilane (15f)



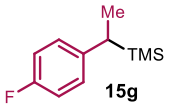
15f

Prepared according to **GP3**, using magnesium tunings (134 mg, 5.5 mmol, 1.1 equiv.), TMSCl (696 µL, 5.5 mmol, 1.1 equiv.) and 1-(1-chloroethyl)-4-chlorobenzene **13f** (746 µL, 5.0 mmol, 1.0 equiv.) in dry THF (20 mL). The crude mixture was purified by flash column chromatography (SiO_2, hexane) to afford silane **15f** (330 mg, 1.6 mmol, 31% yield, 91% purity) as a colorless liquid, containing 9% 1-chloro-4-ethylbenzene inseparable side product.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.07 (m, 2H), 7.00 – 6.85 (m, 2H), 2.14 (q, *J* = 7.5 Hz, 1H), 1.33 (d, *J* = 7.5 Hz, 3H), -0.07 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.67, 133.19, 128.34, 128.17, 29.46, 14.91, -3.47.

(1-(4-Fluorophenyl)ethyl)trimethylsilane (15g)



15g

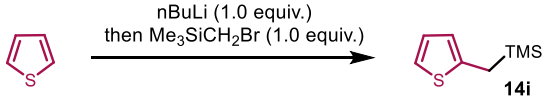
Prepared according to **GP3**, using magnesium tunings (134 mg, 5.5 mmol, 1.1 equiv.), TMSCl (696 µL, 5.5 mmol, 1.1 equiv.) and 1-(1-chloroethyl)-4-fluorobenzene **13g** (793 mg, 5.0 mmol, 1.0 equiv.) in dry THF (20 mL). The crude mixture was purified by flash column chromatography (SiO_2, hexane) to afford silane **15g** (486 mg, 2.5 mmol, 50% yield, 97% purity) as a colorless liquid, containing 3% 1-fluoro-4-ethylbenzene inseparable impurity.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 – 6.90 (m, 4H), 2.14 (q, *J* = 7.5 Hz, 1H), 1.33 (d, *J* = 7.5 Hz, 3H), -0.07 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.43, 159.51, 141.64, 141.61, 128.16, 128.10, 114.88, 114.71, 29.08, 15.16, -3.25.

^{19}F NMR (471 MHz, $CDCl_3$) δ -120.25.

Synthesis of (Thiophen-2-ylmethyl)trimethylsilane (14i)

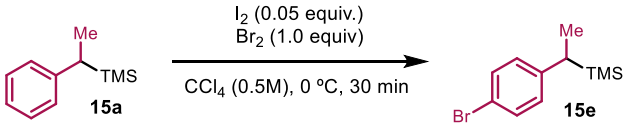


14i

Silane **14i** was prepared according to a reported literature procedure (*54*). To a solution of thiophene (400 µL, 5.00 mmol, 1.0 equiv.) in dry THF (7 mL) at -15 ºC *n*BuLi (2.0 mL, 2.5 N in hexane, 1.0 equiv.) was added dropwise. The solution was stirred for 30 min at -15 ºC. Me,SiCH,Br (714 µL, 5.00 mmol, 1.0 equiv.) was added dropwise and the mixture was allowed to warm up slowly to room temperature and stirred for 16 h. The yellowish solution was treated with cold aqueous NH_4Cl (20 mL) and was extracted with Et_2O (2x25mL). The combined organic layers were washed with water and brine and dried over $MgSO_4$. The solvent was removed *in vacuo*. Silane **14i** (604 mg, 3.6 mmol, 71%) was obtained as yellowish liquid. The silane was used without further purification. The characterization of the title compound was consistent with the data available in the literature (*55*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (dd, *J* = 5.2, 1.2 Hz, 1H), 6.87 (dd, *J* = 5.2, 3.4 Hz, 1H), 6.59 (dq, *J* = 3.3, 1.0 Hz, 1H), 2.29 (s, 2H), 0.04 (s, 9H).

Synthesis of (1-(4-Bromophenyl)ethyl)trimethylsilane (15e)

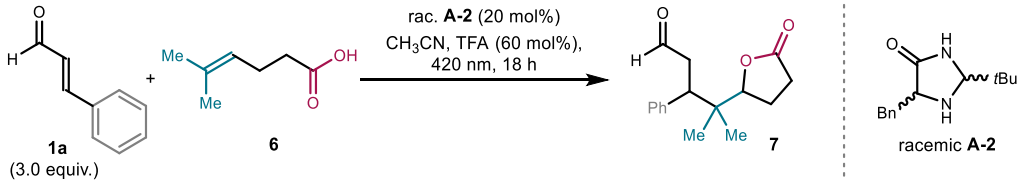


Silane **15e** was prepared according to a reported literature procedure (*56*). To a solution of silane **15a** (1.03 mL, 5.00 mmol, 1.0 equiv.) in CCl_4 (10 mL) at 0 °C I_2 (63 mg, 0.25 mmol, 0.05 equiv.) was added, followed by the dropwise addition of Br_2 (256 µL, 5.0 mmol, 1.0 equiv.). The reaction was stirred for 30 min and then was quenched with aqueous 20% $Na_2S_2O_3$ solution (20 mL). The mixture was extracted with DCM (2x25 mL). The combined organic layers were washed with water and brine and dried with $MgSO_4$. The solvent was removed in vacuo. The crude product was purified by column flash chromatography (SiO_2, hexanes). Silane **15e** (677 mg, 2.63 mmol, 53%) was obtained as colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 2H), 6.93 – 6.87 (m, 2H), 2.13 (q, *J* = 7.5 Hz, 1H), 1.33 (d, *J* = 7.5 Hz, 3H), -0.07 (s, 10H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.22, 131.10, 128.79, 117.79, 29.54, 14.84, -3.27.

Synthesis of 4-Methyl-4-(5-oxotetrahydrofuran-2-yl)-3-phenylpentanal (7)

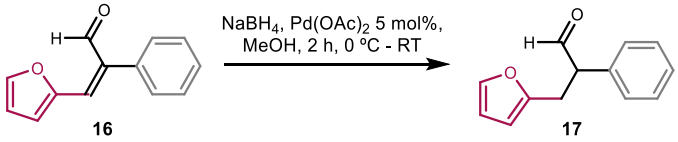


Reference compounds **7** was synthesized following a reported literature procedure (*32*). A dry vial was charged with cinnamaldehyde **1a** (75.5 µL, 0.6 mmol, 3.0 equiv.), 5-methylhex-4-enoic acid **6** (25.6 mg, 0.2 mmol, 1.0 equiv.) and racemic amine catalyst **A-2** (9.9 mg, 40 µmol, 20 mol%). The vial was sealed with a septum, flushed with argon, dry acetonitrile (400 µL) and TFA (9.2 µL, 0.12 mmol, 60 mol%) was added and the vial was stirred for 18 h under irradiation with 420 nm (single LED, 120 mW/cm^3) under ambient conditions. The crude mixture was purified by flash column chromatography (SiO_2, hexane:EtOAc 70:30) to afford the lactone product **7** (45.8 mg, 0.18 mmol, 88% yield, 1:1 d.r.) as a mixture of two diastereomers. The corresponding 2,4-dinitrophenylhydrazones (obtained upon condensation with 2,4-dinitrophenylhydrazine) could be separated by preparative TLC and the enantiomers could be separated by UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 70:30 CO_2/EtOH for 5 min; isocratic 70:30 CO_2/EtOH for 9 min, gradient from 70:30 CO_2/EtOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 346 nm: **7**: diastereomer 1: τ = 9.6 min and τ = 11.8 min, diastereomer 2: τ = 10.8 min and τ = 11.2 min.

^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereoisomers) δ 9.51 (dd, *J* = 2.6, 1.2 Hz, 1H), 9.49 (dd, *J* = 2.9, 1.5 Hz, 1H), 7.34 – 7.18 (m, 10H), 4.28 (dd, *J* = 8.8, 7.0 Hz, 1H), 4.09 (dd, *J* = 8.8, 7.3 Hz, 1H), 3.52 (dd, *J* = 10.6, 5.0 Hz, 1H), 3.34 (dd, *J* = 10.9, 4.3 Hz, 1H), 3.04 (ddd, *J* = 17.0, 10.9, 2.6 Hz, 1H), 2.96 – 2.76 (m, 3H), 2.57 – 2.39 (m, 4H), 2.17 – 1.91 (m, 4H), 1.03 (s, 3H), 0.96 (s, 3H), 0.87 (s, 3H), 0.78 (s, 3H).

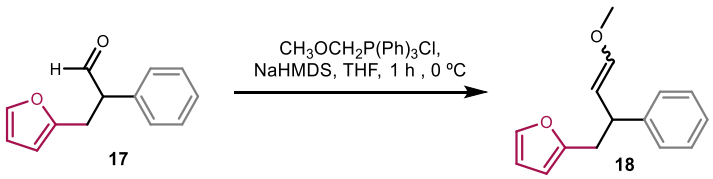
Synthesis of 2-(4-Methoxy-2-phenylbut-3-en-1-yl)furan (18) for the Determination of Enantiomeric Ratio of 3j

3-(Furan-2-yl)-2-phenylpropanal (17)



The procedure was adapted from a literature procedure (*58*). A dry round bottom flask, equipped with magnet a septum and 3 empty balloons was charged under Argon atmosphere with 3-(2-furyl)-2-phenylpropenal **16** (594 mg, 3.0 mmol, 1.0 equiv.), $NaBH_4$ (113 mg, 3.0 mmol, 1.0 equiv.) and $Pd(OAc)_2$ (33.7 mg, 5 mol%). The flask was cooled to 0 °C and dry methanol (3 mL) was carefully added dropwise (evolution of hydrogen!). The ice bath was removed and the mixture was stirred for 2 h, filtered over celite and concentrated. The residue was redissolved in DCM (50 mL) and washed with brine. The organic layer was dried with $MgSO_4$, filtered and concentrated. Column chromatography (SiO_2, hexane:EtOAc 9:1) afforded aldehyde **17** (40 mg, 0.20 mmol, 7%) as colorless oil (side product).
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.75 (d, *J* = 1.4 Hz, 1H), 7.41 – 7.33 (m, 2H), 7.32 – 7.27 (m, 2H), 7.19 – 7.15 (m, 2H), 6.22 (dd, *J* = 3.2, 1.9 Hz, 1H), 5.91 (dd, *J* = 3.2, 0.8 Hz, 1H), 3.98 (td, *J* = 7.3, 1.4 Hz, 1H), 3.47 (dd, *J* = 15.5, 7.1 Hz, 1H), 3.04 (dd, *J* = 15.4, 7.5 Hz, 1H).
^{13}C NMR (126 MHz, $CDCl_3$): δ 199.49, 152.59, 141.41, 135.53, 129.22, 128.91, 127.95, 110.37, 106.87, 57.80, 28.64.
HRMS (ESI): calculated for $[M+Na]^+$ $[C_{13}H_{12}NaO_2]^+$: 223.0730, found 223.0724.

2-(4-Methoxy-2-phenylbut-3-en-1-yl)furan (18)



A dry flask was charged with methoxymethyl-triphenylphosphonium chloride (249 mg, 0.729 mmol, 3.9 equiv.) under an argon atmosphere and anhydrous THF (3 mL) was added. After cooling to 0 °C, NaHMDS (0.73 mL, 0.73 mmol, 3.9 equiv., 1 M in THF) was added and the mixture was stirred for 10 minutes. Then, a solution of aldehyde **17** (40 mg, 0.187 mmol, 1 equiv.) in anhydrous THF (2 mL) was added and the mixture was stirred for 1 h at 0 °C. The mixture was filtered over a plug of silica gel (afterwash with ethylacetate) and concentrate. Column chromatography (SiO_2, hexane:EtOAc 95:5) afforded 2.2 mg (5%) of enol ether **18** (2.2 mg, 9.6 µmol, 5%, 4:1 mixture of double bond isomers). The enantiomers of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) were separated by UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/*i*-PrOH for 5 min; isocratic 60:40 CO_2/*i*-PrOH for 2 min, gradient from 60:40 CO_2/*i*-PrOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 347 nm, **3j**: τ = 6.0 min and τ = 6.1 min.

^{1}H NMR (500 MHz, $CDCl_3$, *major isomer*): δ 7.32 – 7.14 (m, 6H), 6.25 (d, *J* = 12.6 Hz, 1H), 6.22 (dd, *J* = 3.2, 1.9 Hz, 1H), 5.87 (dd, *J* = 3.1, 0.7 Hz, 1H), 4.94 (dd, *J* = 12.6, 8.5 Hz, 1H), 3.66 – 3.57 (m, 1H), 3.48 (s, 3H), 3.07 – 2.92 (m, 2H).
^{13}C NMR (126 MHz, $CDCl_3$, *mixture of isomers*): δ 154.62154.20, 147.98, 146.40, 144.90, 141.00, 140.89, 128.56, 128.48, 127.42, 127.35, 126.41, 126.19, 110.21, 110.14, 109.70, 106.53, 106.33, 106.08, 77.41, 77.16, 76.91, 59.81, 56.11, 43.86, 39.53, 36.11, 35.58.
HRMS (ESI): calculated for $[M+Na]^+$ $[C_{15}H_{16}NaO_2]^+$: 251.1043, found: 251.1053.

I. General Procedures and Scope of the Biocatalytic Radical Coupling

I.1 Experimental Setup

Set-up:

The biocatalytic reactions were performed using a violet LED strip as the light source. A commercial 5-meter LED strip was wrapped around a 9 cm crystallizing dish, while a fan was used to cool down the reactor (the reaction temperature was measured to be between 28-33 ºC). The experiments at 405 nm were conducted using a 5 m strip, from Arotelicht, model number: 5M SMD 2835 LED purchased from Amazon.

Analytical scale (Set-up 1): The set up for the analytical scale consisted of a crystallizing dish with a 3D printed support of 10 positions, and a hole of 47 mm in the middle to allow ventilation (**Figure S16**, left). Each of the positions could be used to fit a standard 16 mm diameter vial.

Semipreparative scale (Set-up 2): A 50 mL round bottom flask was placed in the middle of the photoreactor (**Figure S16**, right).

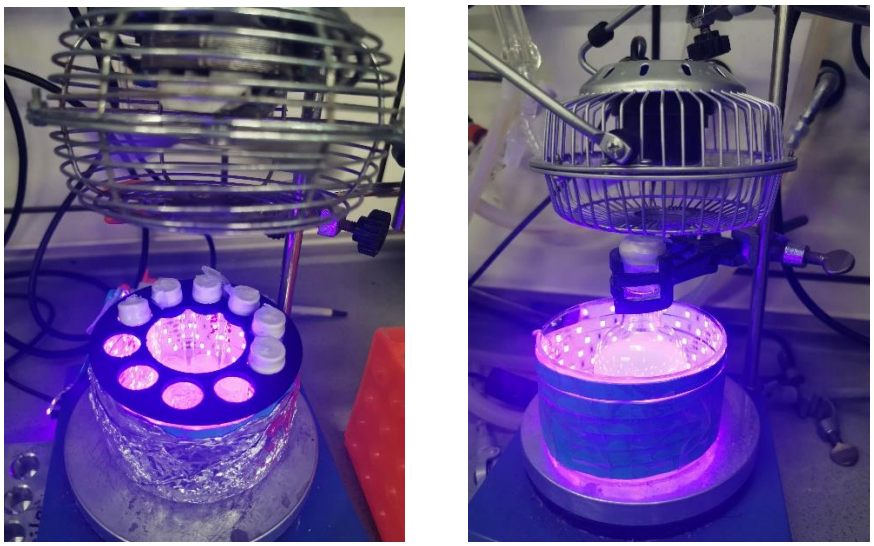
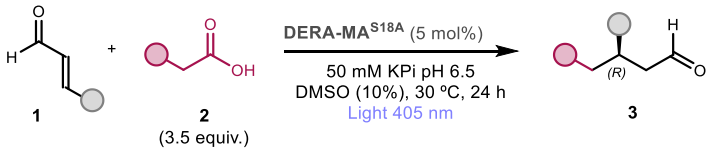


Figure S16. Left panel: *Set-up 2* for the analytical scale enzymatic reactions (1.25 µmol scale) right panel: *Set-up 2* for the semi-preparative scale enzymatic reactions (0.075 mmol scale)

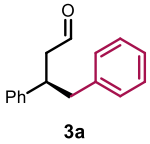
I.2 Analytical Scale Biocatalytic Reactions – Enantioselective Procedure

GP4 – General Procedure for the Analytical Scale Biocatalytic Synthesis of Compounds 3



A stock solution of enal **1** (50 mM) and a stock solution of the corresponding acid **2** (175 mM) in DMSO were added to a 5 mL glass vial containing KPi buffer pH 6.5. The headspace of the vial was purged with argon and the purified enzyme DERA-MA^{S18A} (62.5 nmol, 0.05 equiv.) in KPi buffer pH 6.5 was added to reach the final volume of 500 µL. The vial was then placed in the 3D printed support photoreactor (see section I1) and irradiated under stirring (5 mm x 2 mm, VWR, 360 rpm) for 16 hours. The crude mixture was extracted once with 600 µL ethyl acetate containing 5 mM of the internal standard 1,3,5-trimethoxybenzene. The organic extract was dried over anhydrous $MgSO_4$, filtered and analyzed by GC-FID on HP-5 column. Calibration curves were obtained using the previously synthesized reference compounds **3** and 1,3,5-trimethoxybenzene as the internal standard. The GC-FID data for the analytical scale reactions were fit in the equation to determine the conversion (analytical yield) and diastereomeric ratio of the products **3**. The enantiomeric excess was determined by UPC^2 analysis.

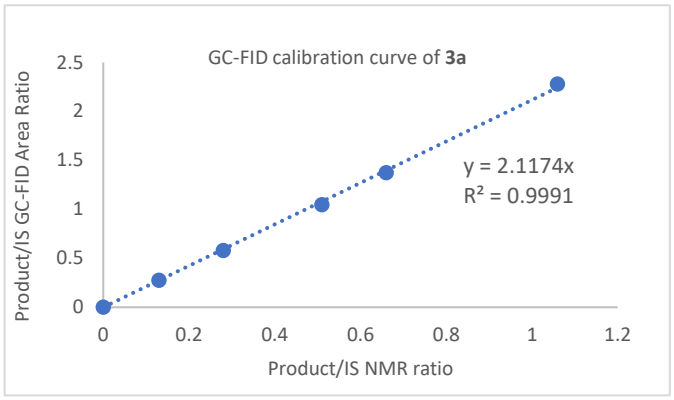
(*R*)-3,4-Diphenylbutanal (3a)



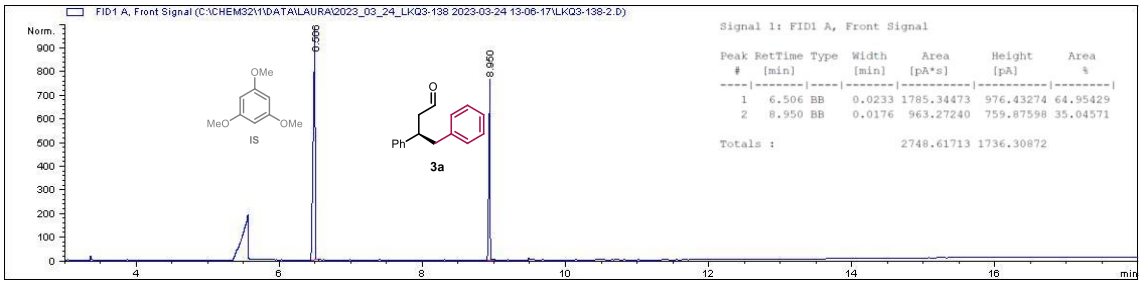
3a

Prepared according to **GP4**, using phenylacetic acid **2a** (25 µL of a 175 mM stock solution in DMSO, 4.4 µmol) and cinnamaldehyde **1a** (25 µL of a 50 mM stock solution in DMSO, 1.25 µmol) as substrates in a 10% v/v DMSO/KPi buffer pH 6.5 mixture. The crude extract was analyzed by GC-FID on HP-5 column. The conversion (analytical yield) of product **3a** was determined according to the calibration curve given below using 1,3,5-trimethoxybenzene as the internal standard and as an average of three runs (57% yield, >99% ee). The enantiomeric excess of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) was determined using UPC^2 on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/*i*-PrOH for 5 min; isocratic 60:40 CO_2/*i*-PrOH for 2 min, gradient from 60:40 CO_2/*i*-PrOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 347 nm, **3a**: τ_{major} = 6.4 min and τ_{minor} = 6.5 min. The absolute configuration was assigned by comparison of the enzymatic product with the corresponding product **3a** obtained via the organocatalytic route (*34*, see Section E3).

a)



b)



c)

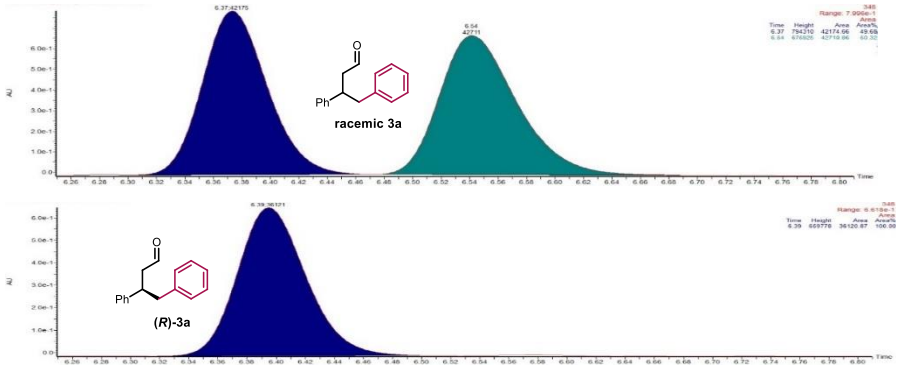
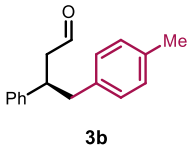


Figure S17. (a) Calibration curve of compound **3a**, (b) GC-FID analysis for determination of the conversion (analytical yield) of the enzymatic reaction, and (c) UPC^2 analysis for determination of the ee. GC-FID calibration curves were obtained from 5mM solutions of the internal standard (IS = 1,3,5-trimethoxybenzene) in ethyl acetate with different concentrations of the corresponding product **3a**.

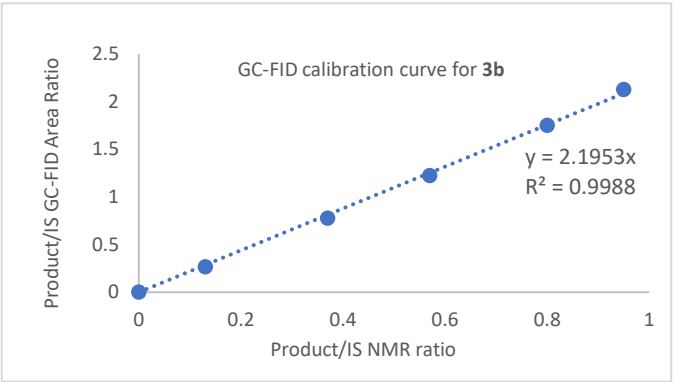
(*R*)-3-Phenyl-4-(p-tolyl)butanal (3b)



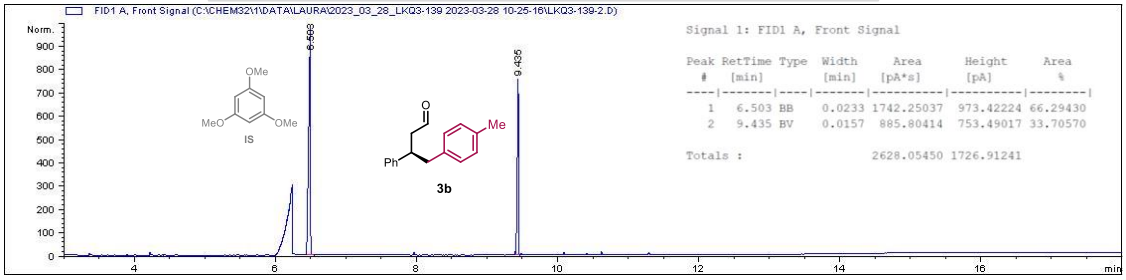
3b

Prepared according to **GP4**, using p-tolylacetic acid **2b** (25 µL of a 175 mM stock solution in DMSO, 4.4 µmol) and cinnamaldehyde **1a** (25 µL of a 50 mM stock solution in DMSO, 1.25 µmol) as substrates in a 10% v/v DMSO/KPi buffer pH 6.5 mixture. The crude extract was analyzed by GC-FID on HP-5 column. The analytical yield of product **3b** was determined according to the calibration curve given below using 1,3,5-trimethoxybenzene as the internal standard and as an average of three runs (53% yield, >99% ee). The enantiomeric excess of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) was determined using UPC^2 on a Daicel Chiralpak ID-3 column isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/i-PrOH for 5 min; isocratic 60:40 CO_2/i-PrOH for 2 min, gradient from 60:40 CO_2/i-PrOH to 100% CO_2, flow rate 2.0 mL/min, λ = 348 nm, **3b**: τ_{major} = 6.3 min and τ_{minor} = 6.5 min.

a)



b)



c)

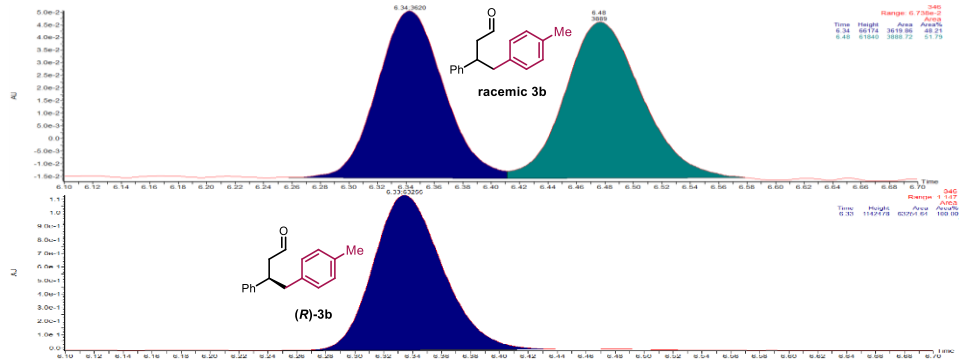
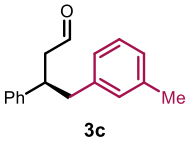


Figure S18. (a) Calibration curve of compound **3b**, (b) GC-FID analysis for determination of the conversion (analytical yield) of the enzymatic reaction, and (c) UPC^2 analysis for determination of the ee. GC-FID calibration curves were obtained from 5mM solutions of the internal standard (IS = 1,3,5-trimethoxybenzene) in ethyl acetate with different concentrations of the corresponding product **3b**.

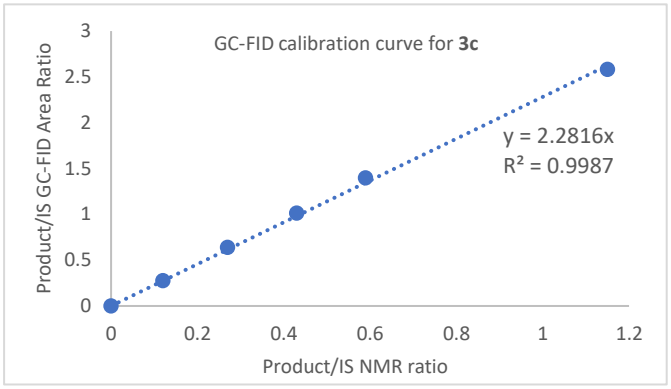
(*R*)-3-Phenyl-4-(*m*-tolyl)butanal (3c)



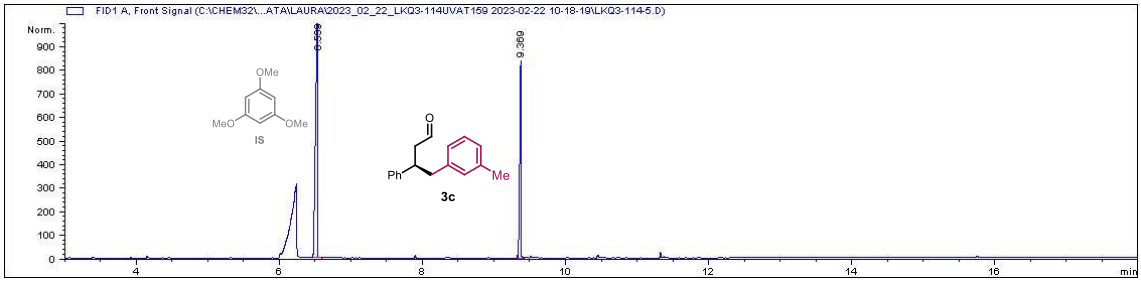
3c

Prepared according to **GP4**, using *m*-tolylacetic acid **2c** (25 µL of a 175 mM stock solution in DMSO, 4.4 µmol) and cinnamaldehyde **1a** (25 µL of a 50 mM stock solution in DMSO, 1.25 µmol) as substrates in a 10% v/v DMSO/KPi buffer pH 6.5 mixture. In this case, parental enzyme DERA-MA (62.5 nmol, 0.05 equiv.) was added. The crude extract was analyzed by GC-FID on HP-5 column. The analytical yield of product **3c** was determined according to the calibration curve given below using 1,3,5-trimethoxybenzene as the internal standard and as an average of three runs (53% yield, >99% ee). The enantiomeric excess of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) was determined using UPC^2 on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/i-PrOH for 5 min; isocratic 60:40 CO_2/i-PrOH for 2 min, gradient from 60:40 CO_2/i-PrOH to 100% CO_2, flow rate 2.0 mL/min, λ = 348 nm, **3c**: τ_{major} = 6.3 min and τ_{minor} = 6.4 min.

a)



b)



c)

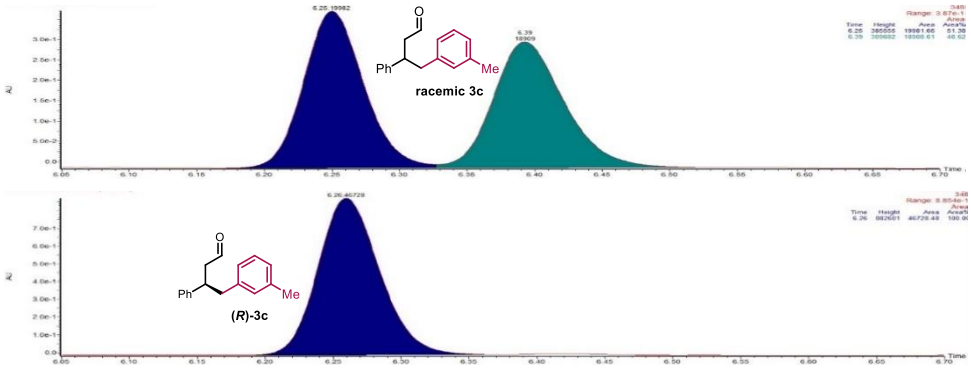
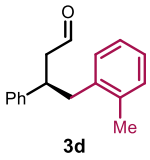


Figure S19. (a) Calibration curve of compound **3c**, (b) GC-FID analysis for determination of the conversion (analytical yield) of the enzymatic reaction, and (c) UPC^2 analysis for determination of the ee. GC-FID calibration curves were obtained from 5mM solutions of the internal standard (IS = 1,3,5-trimethoxybenzene) in ethyl acetate with different concentrations of the corresponding product **3c**.

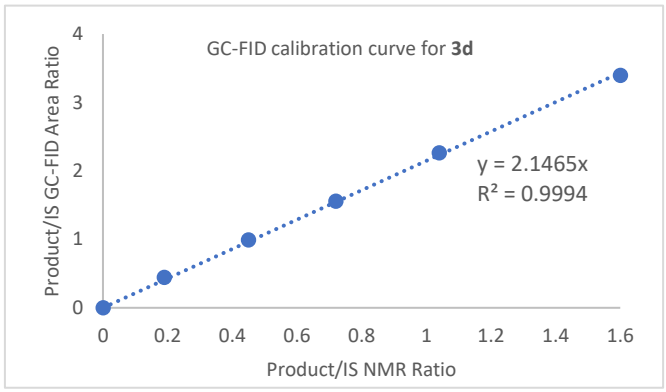
(*R*)-3-Phenyl-4-(*o*-tolyl)butanal (3d)



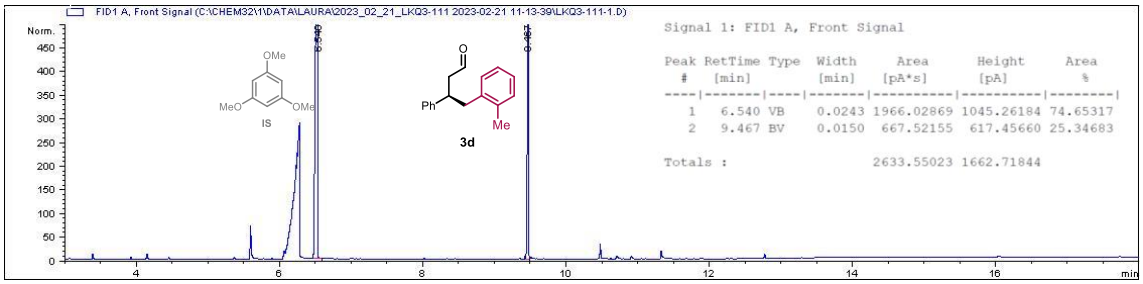
3d

Prepared according to **GP4**, using *o*-tolylacetic acid **2d** (25 µL of a 175 mM stock solution in DMSO, 4.4 µmol) and cinnamaldehyde **1a** (25 µL of a 50 mM stock solution in DMSO, 1.25 µmol) as substrates in a 10% v/v DMSO/KPi buffer pH 6.5 mixture. In this case, parental enzyme DERA-MA (62.5 nmol, 0.05 equiv.) was added. The crude extract was analyzed by GC-FID on HP-5 column. The analytical yield of product **3d** was determined according to the calibration curve given below using 1,3,5-trimethoxybenzene as the internal standard and as an average of three runs (35% yield, 99% ee). The enantiomeric excess of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) was determined by UPC^2 analysis on a Daicel Chiralpak ID-3 column isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/i-PrOH for 5 min; isocratic 60:40 CO_2/i-PrOH for 2 min, gradient from 60:40 CO_2/i-PrOH to 100% CO_2, flow rate 2.0 mL/min, λ = 348 nm, **3d**: τ_{major} = 6.3 min and τ_{minor} = 6.5 min.

a)



b)



c)

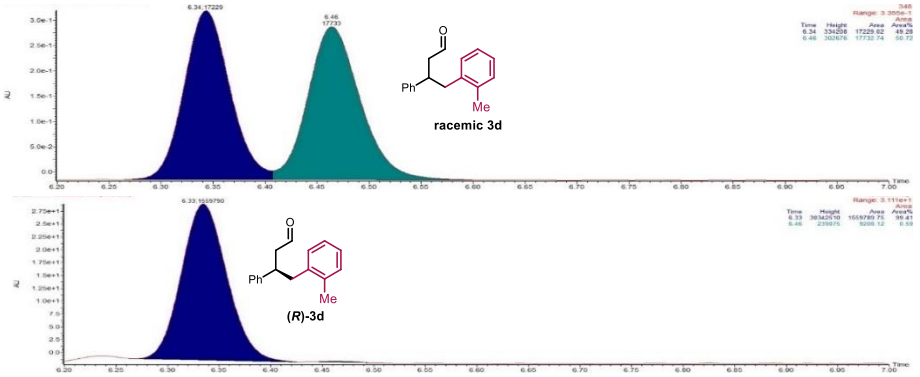
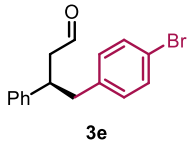


Figure S20. (a) Calibration curve of compound **3d**, (b) GC-FID analysis for determination of the conversion (analytical yield) of the enzymatic reaction, and (c) UPC^2 analysis for determination of the ee. GC-FID calibration curves were obtained from 5mM solutions of the internal standard (IS = 1,3,5-trimethoxybenzene) in ethyl acetate with different concentrations of the corresponding product **3d**.

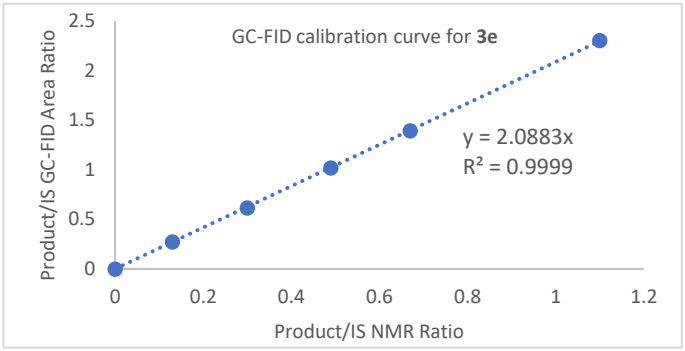
(*R*)-4-(4-Bromophenyl)-3-phenylbutanal (3e)



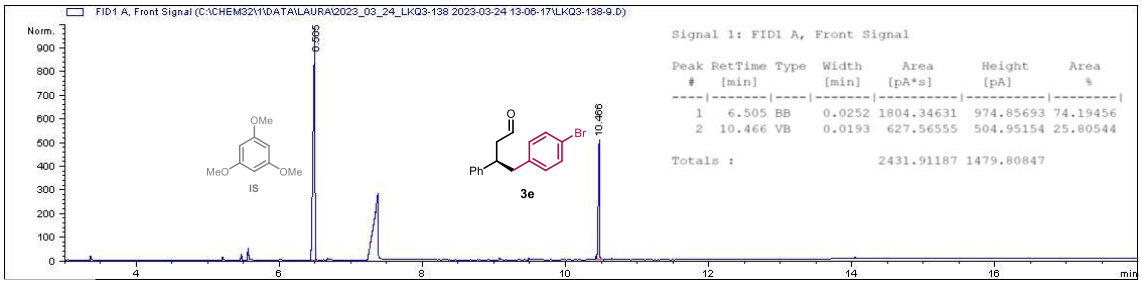
3e

Prepared according to **GP4**, using 4-bromophenylacetic acid **2e** (25 µL of a 175 mM stock solution in DMSO, 4.4 µmol) and cinnamaldehyde **1a** (25 µL of a 50 mM stock solution in DMSO, 1.25 µmol) as substrates in a 10% v/v DMSO/KPi buffer pH 6.5 mixture. The crude extract was analyzed by GC-FID on HP-5 column. The analytical yield of product **3e** was determined according to the calibration curve given below using 1,3,5-trimethoxybenzene as the internal standard and as an average of three runs (37% yield, >99% ee). The enantiomeric excess of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) was determined by UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/i-PrOH for 5 min; isocratic 60:40 CO_2/i-PrOH for 2 min, gradient from 60:40 CO_2/i-PrOH to 100% CO_2, flow rate 2.0 mL/min, λ = 347 nm, **3e**: τ_{major} = 7.3 min and τ_{minor} = 7.6 min.

a)



b)



c)

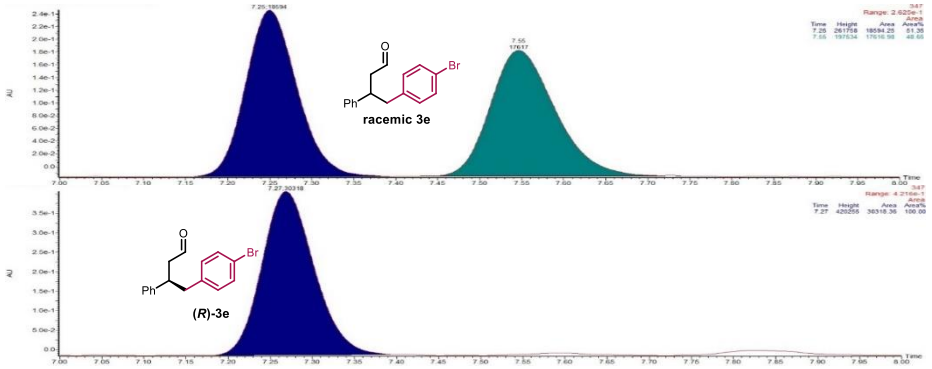
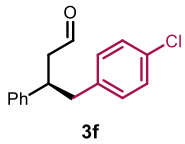


Figure S21. (a) Calibration curve of compound **3e**, (b) GC-FID analysis for determination of the conversion (analytical yield) of the enzymatic reaction, and (c) UPC^2 analysis for determination of the ee. GC-FID calibration curves were obtained from 5mM solutions of the internal standard (IS = 1,3,5-trimethoxybenzene) in ethyl acetate with different concentrations of the corresponding product **3e**.

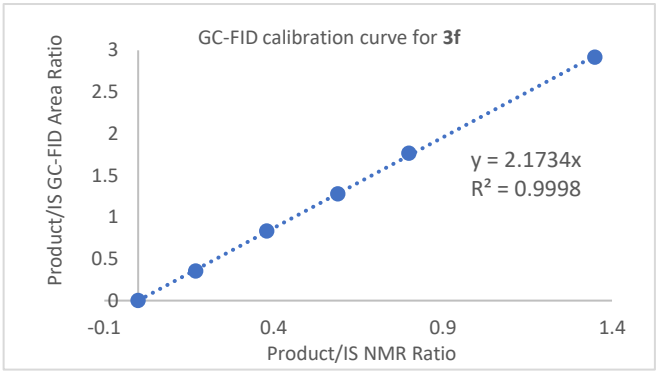
(*R*)-4-(4-Chlorophenyl)-3-phenylbutanal (3f)



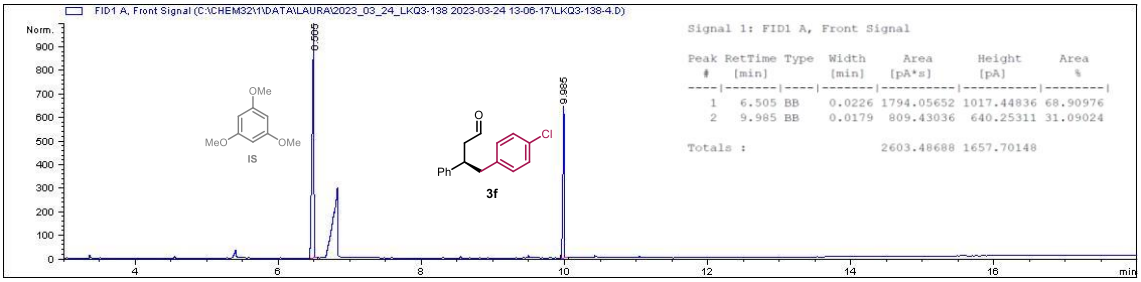
3f

Prepared according to **GP4**, using 4-chlorophenylacetic acid **2f** (25 µL of a 175 mM stock solution in DMSO, 4.4 µmol) and cinnamaldehyde **1a** (25 µL of a 50 mM stock solution in DMSO, 1.25 µmol) as substrates in a 10% v/v DMSO/KPi buffer pH 6.5 mixture. The crude extract was analyzed by GC-FID on HP-5 column. The analytical yield of product **3f** was determined according to the calibration curve given below using 1,3,5-trimethoxybenzene as the internal standard and as an average of three runs (46% yield, >99% ee). The enantiomeric excess of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) was determined by UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/i-PrOH for 5 min; isocratic 60:40 CO_2/i-PrOH for 2 min, gradient from 60:40 CO_2/i-PrOH to 100% CO_2, flow rate 2.0 mL/min, λ = 347 nm, **3f**: τ_{major} = 6.9 min and τ_{minor} = 7.1 min.

a)



b)



c)

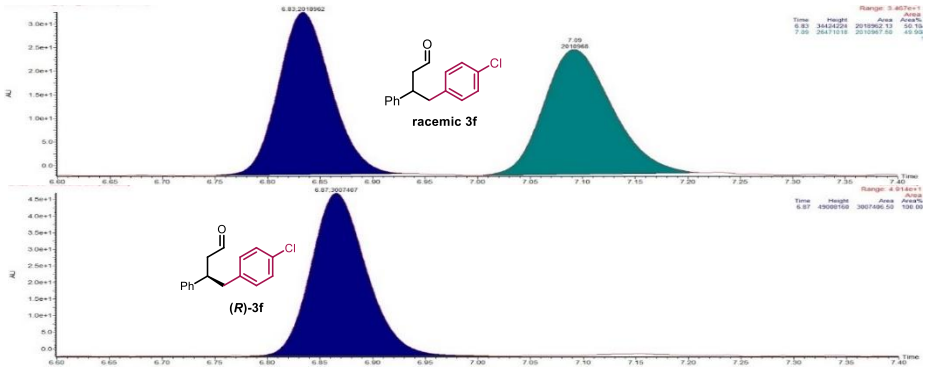
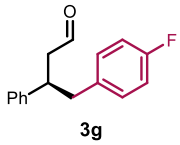


Figure S22. (a) Calibration curve of compound **3f**, (b) GC-FID analysis for determination of the conversion (analytical yield) of the enzymatic reaction, and (c) UPC^2 analysis for determination of the ee. GC-FID calibration curves were obtained from 5mM solutions of the internal standard (IS = 1,3,5-trimethoxybenzene) in ethyl acetate with different concentrations of the corresponding product **3f**.

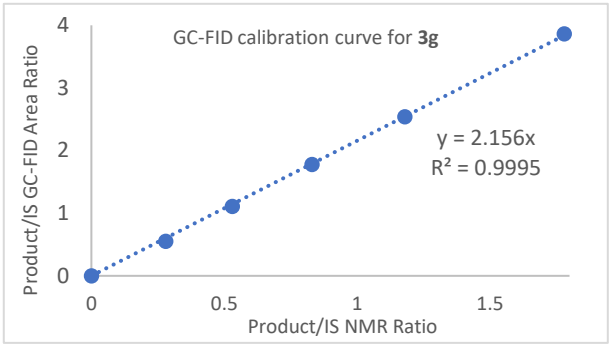
(*R*)-4-(4-Fluorophenyl)-3-phenylbutanal (3g)



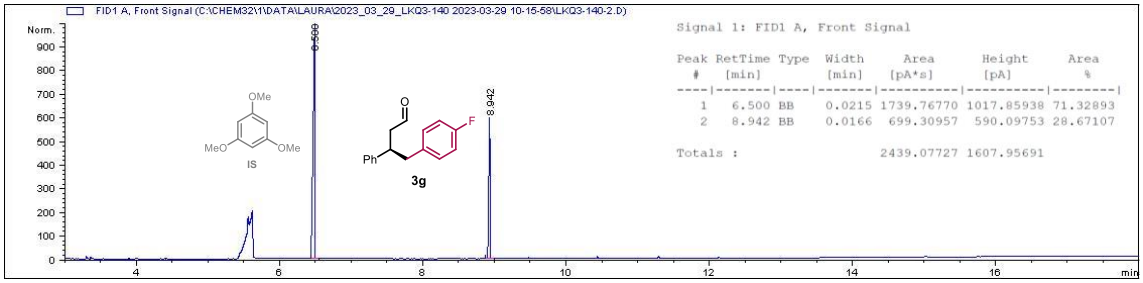
3g

Prepared according to **GP4**, using 4-fluorophenylacetic acid **2g** (25 µL of a 175 mM stock solution in DMSO, 4.4 µmol) and cinnamaldehyde **1a** (25 µL of a 50 mM stock solution in DMSO, 1.25 µmol) as substrates in a 10% v/v DMSO/KPi buffer pH 6.5 mixture. The crude extract was analyzed by GC-FID on HP-5 column. The analytical yield of product **3g** was determined according to the calibration curve given below using 1,3,5-trimethoxybenzene as the internal standard and as an average of three runs (43% yield, >99% ee). The enantiomeric excess of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) was determined by UPC^2 analysis on a Daicel Chiralpak ID-3 column isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/*i*PrOH for 5 min; isocratic 60:40 CO_2/*i*PrOH for 2 min, gradient from 60:40 CO_2/*i*-PrOH to 100% CO_2, flow rate 2.0 mL/min, λ = 347 nm, **3g**: τ_{major} = 6.2 min and τ_{minor} = 6.5 min.

a)



b)



c)

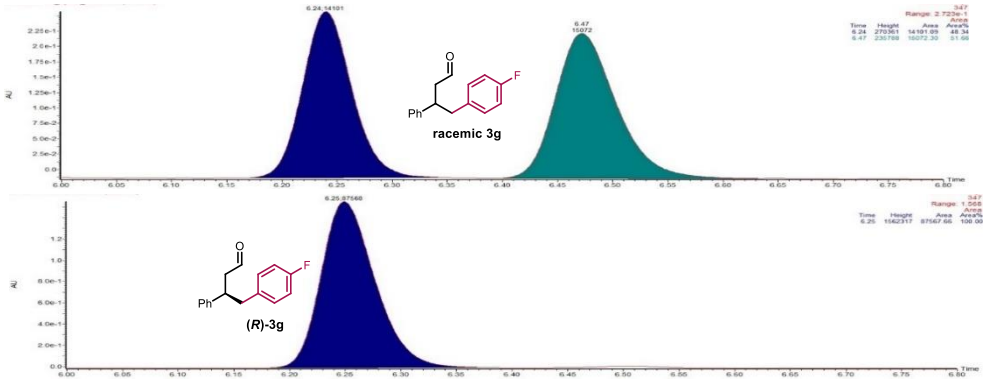
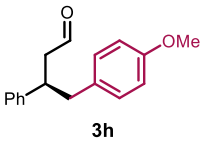


Figure S23. (a) Calibration curve of compound **3g**, (b) GC-FID analysis for determination of the conversion (analytical yield) of the enzymatic reaction, and (c) UPC^2 analysis for determination of the ee. GC-FID calibration curves were obtained from 5mM solutions of the internal standard (IS = 1,3,5-trimethoxybenzene) in ethyl acetate with different concentrations of the corresponding product **3g**.

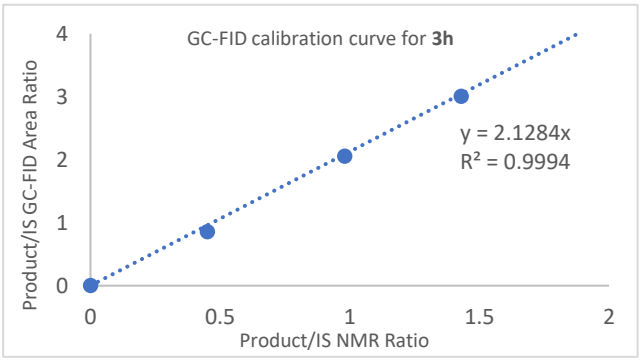
(*R*)-4-(4-Methoxyphenyl)-3-phenylbutanal (3h)



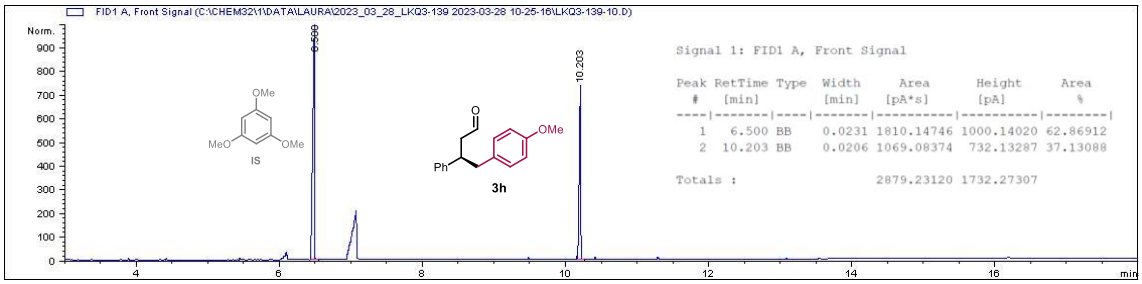
3h

Prepared according to **GP4**, using 4-methoxyphenylacetic acid **2h** (25 µL of a 175 mM stock solution in DMSO, 4.4 µmol) and cinnamaldehyde **1a** (25 µL of a 50 mM stock solution in DMSO, 1.25 µmol) as substrates in a 10% v/v DMSO/KPi buffer pH 6.5 mixture. The crude extract was analyzed by GC-FID on HP-5 column. The analytical yield of product **3h** was determined according to the calibration curve given below using 1,3,5-trimethoxybenzene as the internal standard and as an average of three runs (61% yield, >99% ee). The enantiomeric excess of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) was determined by UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/*i*PrOH for 5 min; isocratic 60:40 CO_2/*i*PrOH for 2 min, gradient from 60:40 CO_2/*i*PrOH to 100% CO_2, flow rate 2.0 mL/min, λ = 349 nm, **3h**: τ_{major} = 7.0 min and τ_{minor} = 7.2 min.

a)



b)



c)

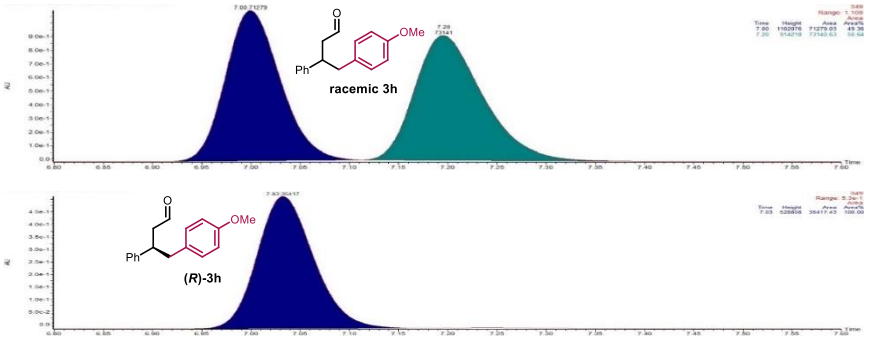
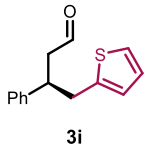


Figure S24. (a) Calibration curve of compound **3h**, (b) GC-FID analysis for determination of the conversion (analytical yield) of the enzymatic reaction, and (c) UPC^2 analysis for determination of the ee. GC-FID calibration curves were obtained from 5mM solutions of the internal standard (IS = 1,3,5-trimethoxybenzene) in ethyl acetate with different concentrations of the corresponding product **3h**.

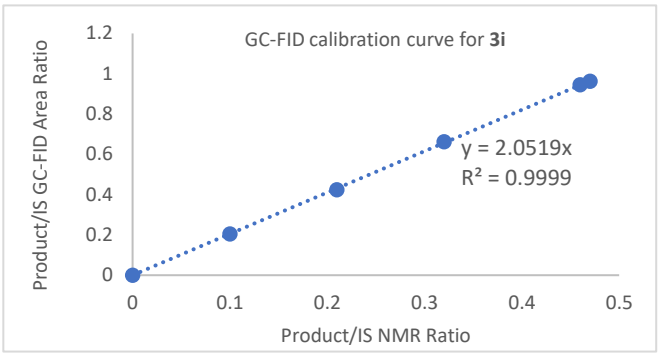
(*R*)-3-Phenyl-4-(thiophen-2-yl)butanal (3i)



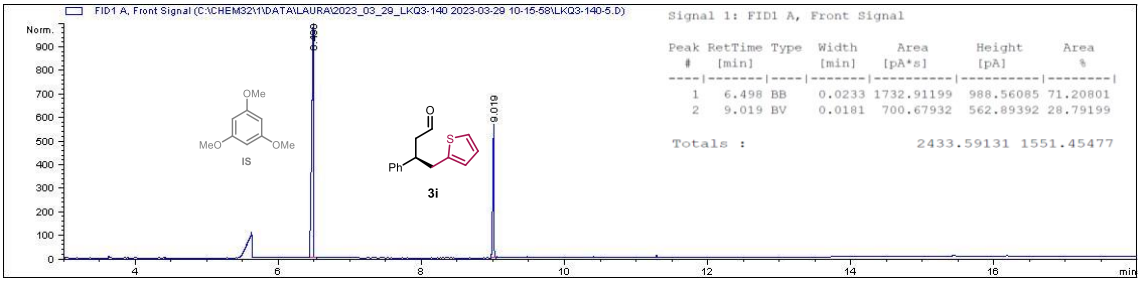
3i

Prepared according to **GP4**, using thiophene-2-acetic acid **2i** (25 µL of a 175 mM stock solution in DMSO, 4.4 µmol) and cinnamaldehyde **1a** (25 µL of a 50 mM stock solution in DMSO, 1.25 µmol) as substrates in a 10% v/v DMSO/KPi buffer pH 6.5 mixture. The crude extract was analyzed by GC-FID on HP-5 column. The analytical yield of product **3i** was determined according to the calibration curve given below using 1,3,5-trimethoxybenzene as the internal standard and as an average of three runs (46% yield, >99% ee). The enantiomeric excess of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) was determined by UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/*i*PrOH for 5 min; isocratic 60:40 CO_2/*i*PrOH for 2 min, gradient from 60:40 CO_2/*i*PrOH to 100% CO_2, flow rate 2.0 mL/min, λ = 348 nm, **3i**: τ_{major} = 6.7 min and τ_{minor} = 6.9 min.

a)



b)



c)

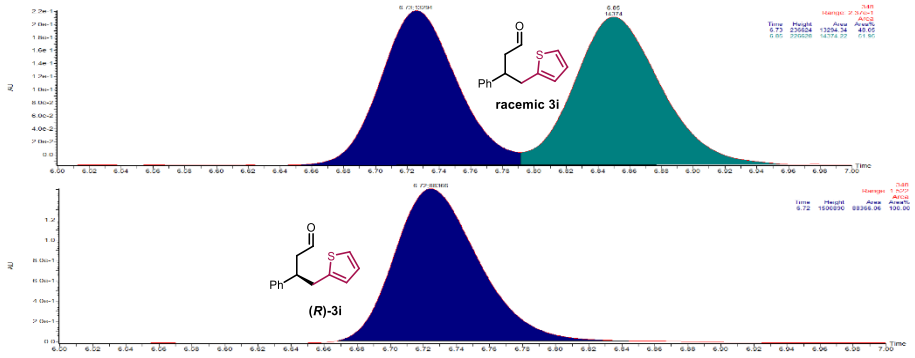
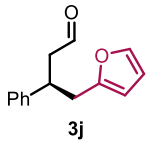


Figure S25. (a) Calibration curve of compound **3i**, (b) GC-FID analysis for determination of the conversion (analytical yield) of the enzymatic reaction, and (c) UPC^2 analysis for determination of the ee. GC-FID calibration curves were obtained from 5mM solutions of the internal standard (IS = 1,3,5-trimethoxybenzene) in ethyl acetate with different concentrations of the corresponding product **3i**.

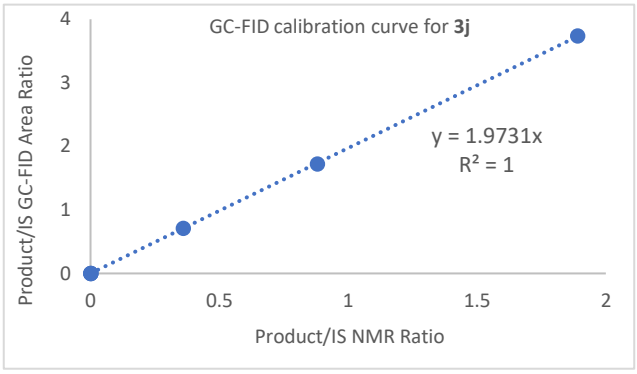
(*R*)-3-Phenyl-4-(furan-2-yl)butanal (3j)



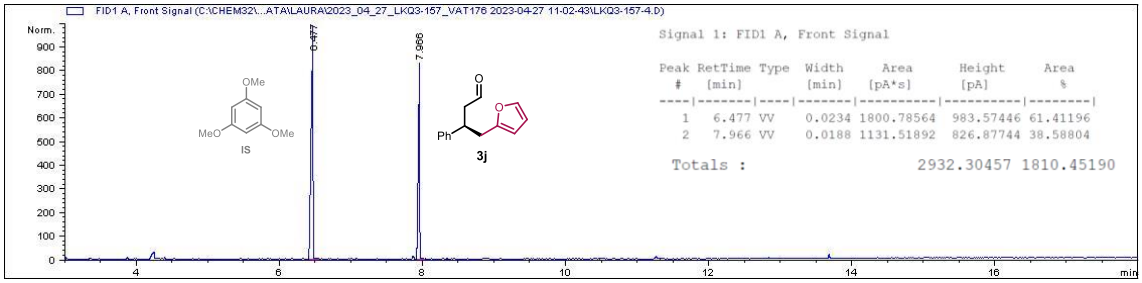
3j

Prepared according to **GP4**, using 2-furanacetic acid **2j** (25 µL of a 175 mM stock solution in DMSO, 4.4 µmol) and cinnamaldehyde **1a** (25 µL of a 50 mM stock solution in DMSO, 1.25 µmol) as substrates in a 10% v/v DMSO/KPi buffer pH 6.5 mixture. The crude extract was analyzed by GC-FID on HP-5 column. The analytical yield of product **3j** was determined according to the calibration curve given below using 1,3,5-trimethoxybenzene as the internal standard and as an average of three runs (71% yield, >99% ee). The enantiomeric excess of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) was determined by UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/*i*PrOH for 5 min; isocratic 60:40 CO_2/*i*PrOH for 2 min, gradient from 60:40 CO_2/*i*PrOH to 100% CO_2, flow rate 2.0 mL/min, λ = 347 nm, **3j**: τ_{major} = 6.0 min and τ_{minor} = 6.1 min.

a)



b)



c)

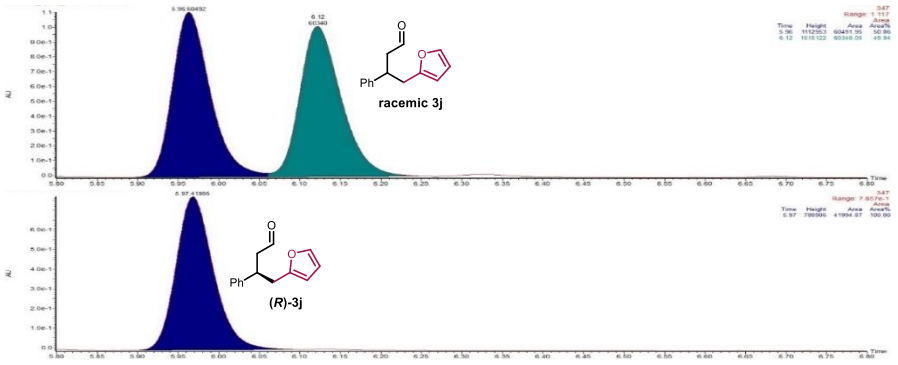
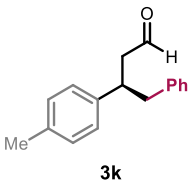


Figure S26. (a) Calibration curve of compound **3j**, (b) GC-FID analysis for determination of the conversion (analytical yield) of the enzymatic reaction, and (c) UPC^2 analysis for determination of the ee. GC-FID calibration curves were obtained from 5mM solutions of the internal standard (IS = 1,3,5-trimethoxybenzene) in ethyl acetate with different concentrations of the corresponding product **3j**.

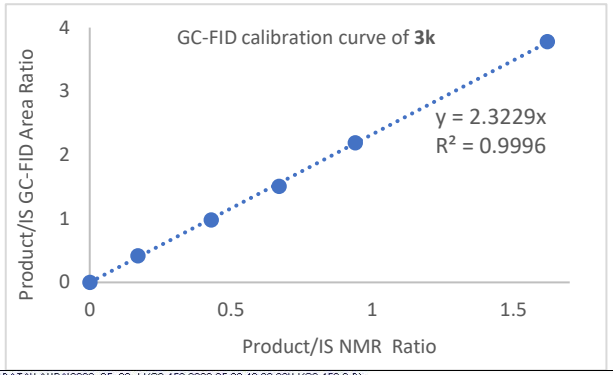
(*R*)-4-Phenyl-3-(p-tolyl)butanal (3k)



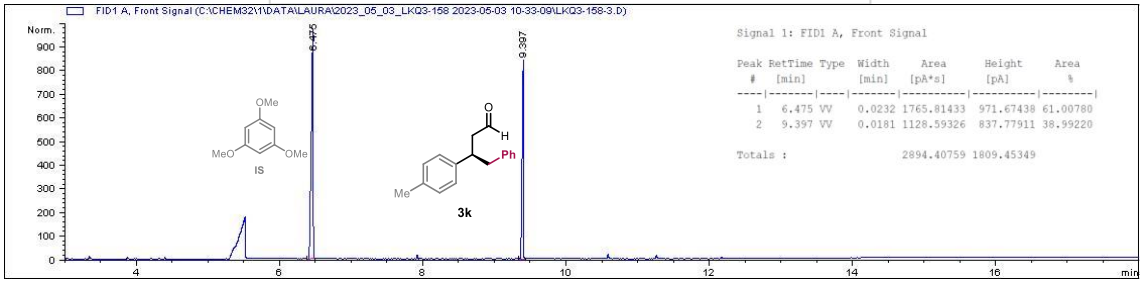
3k

Prepared according to **GP4**, using phenylacetic acid **2a** (25 µL of a 175 mM stock solution in DMSO, 4.4 µmol) and *p*-methylcinnamaldehyde **1b** (25 µL of a 50 mM stock solution in DMSO, 1.25 µmol) as substrates in a 10% v/v DMSO/KPi buffer pH 6.5 mixture. The crude extract was analyzed by GC-FID on HP-5 column. The analytical yield of product **3k** was determined according to the calibration curve given below using 1,3,5-trimethoxybenzene as the internal standard and as an average of three runs (58% yield, >99% ee). The enantiomeric excess of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) was determined using UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/*i*PrOH for 5 min; isocratic 60:40 CO_2/*i*PrOH for 2 min, gradient from 60:40 CO_2/*i*PrOH to 100% CO_2, flow rate 2.0 mL/min, λ = 347 nm, **3k**: τ_{major} = 6.3 min and τ_{minor} = 6.5 min.

a)



b)



c)

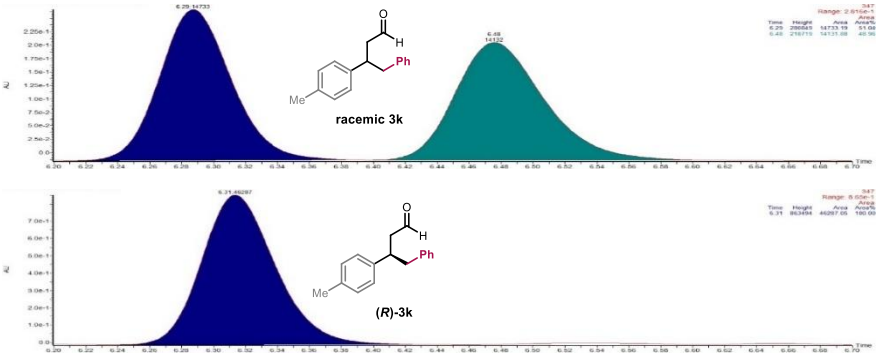
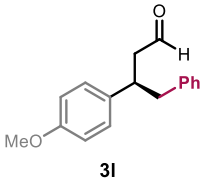


Figure S27. (a) Calibration curve of compound **3k**, (b) GC-FID analysis for determination of the conversion (analytical yield) of the enzymatic reaction, and (c) UPC^2 analysis for determination of the ee. GC-FID calibration curves were obtained from 5mM solutions of the internal standard (IS = 1,3,5-trimethoxybenzene) in ethyl acetate with different concentrations of the corresponding product **3k**.

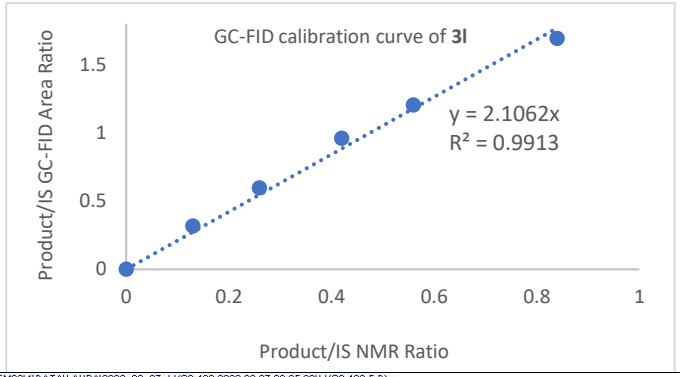
(*R*)-3-(4-Methoxyphenyl)-4-phenylbutanal (3l)



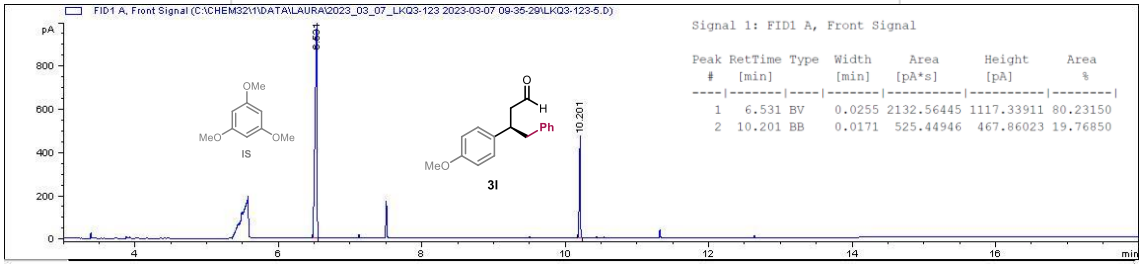
3l

Prepared according to **GP4**, using phenylacetic acid **2a** (25 µL of a 175 mM stock solution in DMSO, 4.4 µmol) and *p*-methoxycinnamaldehyde **1c** (25 µL of a 50 mM stock solution in DMSO, 1.25 µmol) as substrates in a 10% v/v DMSO/KPi buffer pH 6.5 mixture. The crude extract was analyzed by GC-FID on HP-5 column. The analytical yield of product **3l** was determined according to the calibration curve given below using 1,3,5-trimethoxybenzene as the internal standard and as an average of three runs (29% yield, 96% ee). The enantiomeric excess of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) was determined using UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/*i*PrOH for 5 min; isocratic 60:40 CO_2/*i*PrOH for 2 min, gradient from 60:40 CO_2/*i*PrOH to 100% CO_2, flow rate 2.0 mL/min, λ = 348 nm, **3l**: τ_{major} = 6.8 min and τ_{minor} = 7.0 min.

a)



b)



c)

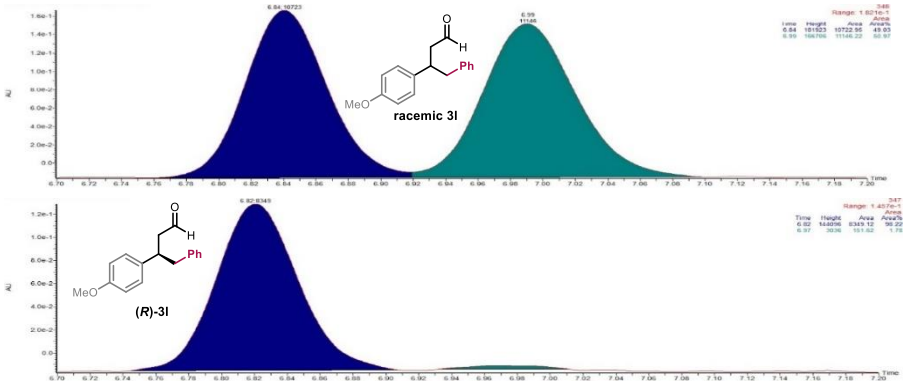
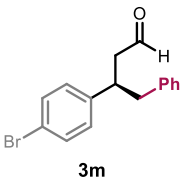


Figure S28. (a) Calibration curve of compound **3l**, (b) GC-FID analysis for determination of the conversion (analytical yield) of the enzymatic reaction, and (c) UPC^2 analysis for determination of the ee. GC-FID calibration curves were obtained from 5mM solutions of the internal standard (IS = 1,3,5-trimethoxybenzene) in ethyl acetate with different concentrations of the corresponding product **3l**.

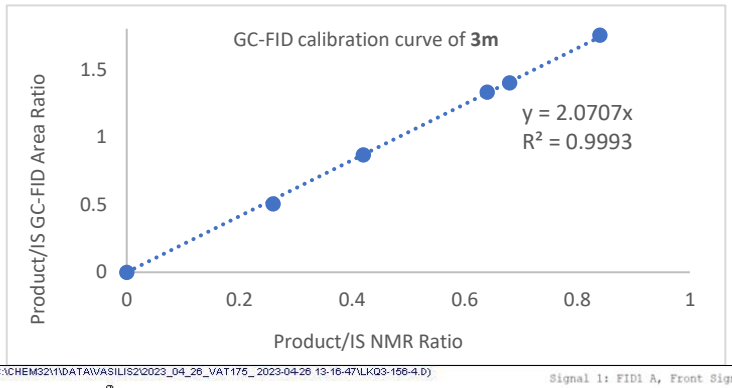
(*R*)-3-(4-Bromophenyl)-4-phenylbutanal (3m)



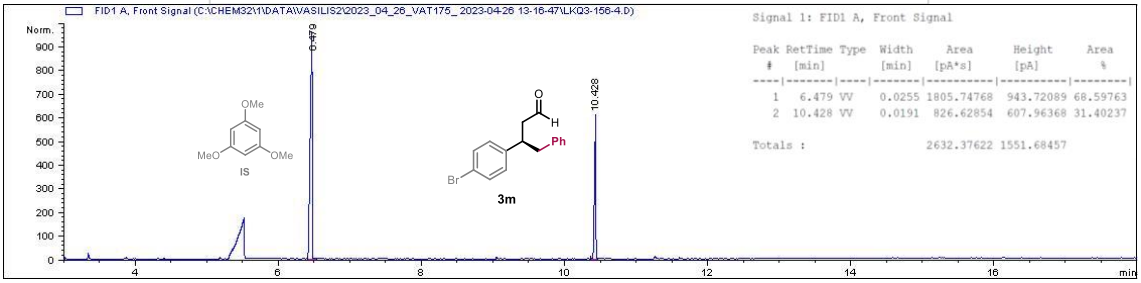
3m

Prepared according to **GP4**, using phenylacetic acid **2a** (25 µL of a 175 mM stock solution in DMSO, 4.4 µmol) and *p*-bromocinnamaldehyde **1d** (25 µL of a 50 mM stock solution in DMSO, 1.25 µmol) as substrates in a 10% v/v DMSO/KPi buffer pH 6.5 mixture. The crude extract was analyzed by GC-FID on HP-5 column. The analytical yield of product **3m** was determined according to the calibration curve given below using 1,3,5-trimethoxybenzene as the internal standard and as an average of three runs (48% yield, >99% ee). The enantiomeric excess of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) was determined using UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/MeOH for 13 min; isocratic 60:40 CO_2/MeOH for 2 min, gradient from 60:40 CO_2/MeOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 350 nm, **3m**: τ_{major} = 13.2 min and τ_{minor} = 13.5 min.

a)



b)



c)

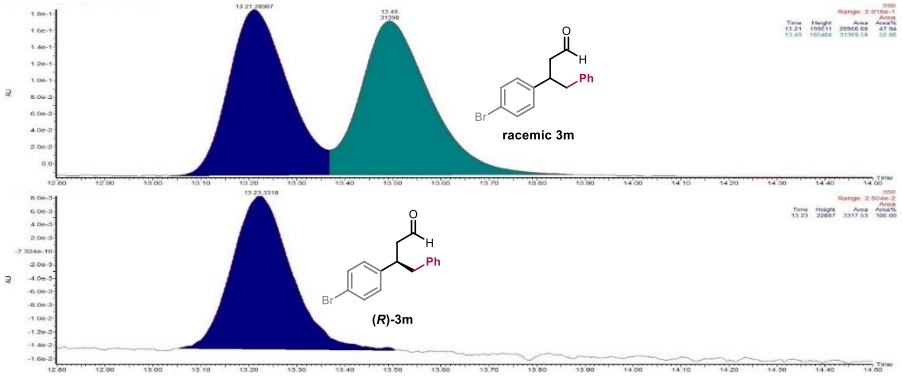
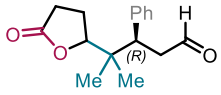


Figure S29. (a) Calibration curve of compound **3m**, (b) GC-FID analysis for determination of the conversion (analytical yield) of the enzymatic reaction, and (c) UPC^2 analysis for determination of the ee. GC-FID calibration curves were obtained from 5mM solutions of the internal standard (IS = 1,3,5-trimethoxybenzene) in ethyl acetate with different concentrations of the corresponding product **3m**.

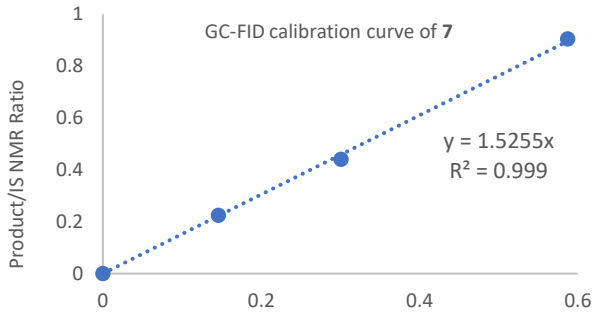
(3*R*)-4-Methyl-4-(5-oxotetrahydrofuran-2-yl)-3-phenylpentanal (7)



7

Prepared according to **GP4**, using 5-methylhex-4-enoic acid **6** (25 µL of a 175 mM stock solution in DMSO, 4.4 µmol) and cinnamaldehyde **1a** (25 µL of a 50 mM stock solution in DMSO, 1.25 µmol) as substrates in a 10% v/v DMSO/KPi buffer pH 6.5 mixture was added. The crude extract was analyzed by GC-FID on HP-5 column. The analytical yield of product **7** was determined according to the calibration curve given below using mesitylene as the internal standard and as an average of three runs (19% yield, 3.8:1 d.r., >99% ee). The enantiomeric excess of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) was determined using UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 70:30 CO_2/EtOH for 5 min; isocratic 70:30 CO_2/EtOH for 9 min, gradient from 70:30 CO_2/EtOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 346 nm: **7**: diastereomer 1: τ = 9.6 min, diastereomer 2: τ = 10.8 min.

a)



b)

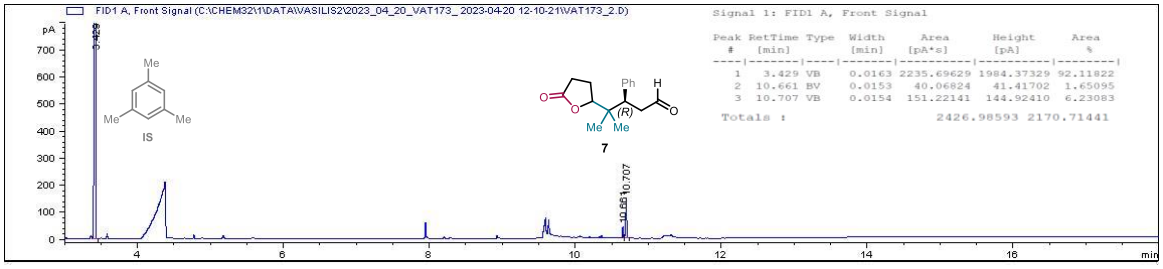


Figure S30. (a) Calibration curve of compound **7**, (b) GC-FID analysis for determination of the conversion (analytical yield) of the enzymatic reaction. GC-FID calibration curves were obtained from 5mM solutions of the internal standard (IS = 1,3,5-trimethoxybenzene) in ethyl acetate with different concentrations of the corresponding product **7**.

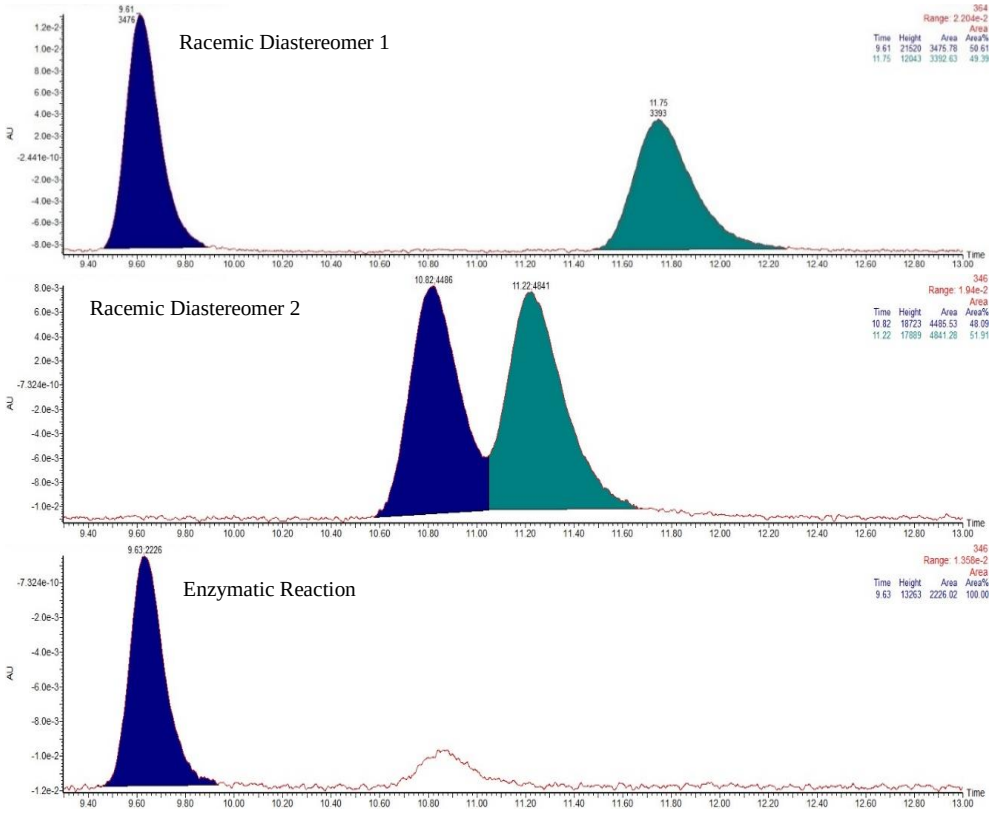
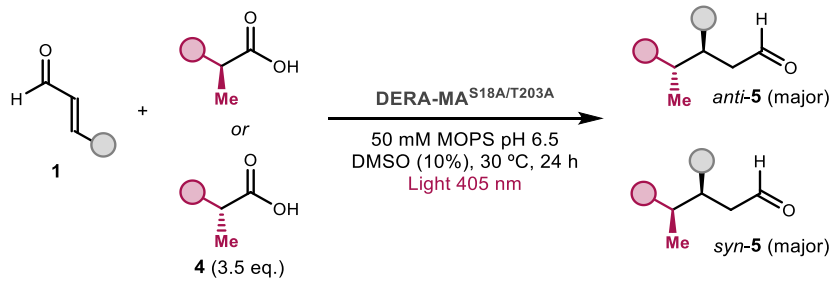


Figure S31. UPC^2 analysis for determination of ee of compound **7**

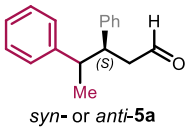
I.3 Analytical Scale Biocatalytic Reactions – Stereospecific Procedure

GP5 – General Procedure for the Analytical Scale the Stereospecific Biocatalytic Synthesis of Compounds 5



A stock solution of enal **1** (50 mM) and a stock solution of the corresponding (*R*)- or (*S*)-acid **4** (175 mM) in DMSO were added to a 5 mL glass vial containing 50 mM MOPS buffer pH 6.5. The headspace of the vial was purged with argon and the purified enzyme DERA-MA$^{S18A/T203A}$ (62.5 nmol, 1.0 equiv.) in MOPS buffer pH 6.5 was added to reach the final volume of 500 µL. The vial was then placed in the 3D printed support photoreactor (see section I1) and irradiated under stirring for 16 hours. The crude mixture was extracted once with 600 µL ethyl acetate containing 5 mM of the internal standard 1,3,5-trimethoxybenzene or mesitylene. The organic extract was dried over anhydrous $MgSO_4$, filtered and analyzed by GC-FID on HP-5 column. Calibration curves were obtained using the previously synthesized reference compounds **5** and internal standard (1,3,5-trimethoxybenzene or mesitylene). The GC-FID data for the analytical scale reactions were fit in the equation to determine the conversion (analytical yield) and diastereomeric ratio of the products **5**. The enantiomeric excess was determined by UPC^2 analysis on chiral stationary phase columns.

(3*S*)-3,4-Diphenylpentanal (5a)



syn- or *anti*-**5a**

Prepared according to **GP5**, using (*R*)- or (*S*)-2-phenylpropionic acid **4a** (25 µL of a 87.5 mM stock solution in DMSO, 2.2 µmol) and cinnamaldehyde **1a** (25 µL of a 25 mM stock solution in DMSO, 0.68 µmol) as substrates in a 10% v/v DMSO/MOPS buffer pH 6.5 mixture. The crude extract was analyzed by GC-FID on HP-5 column. The analytical yield of product **5a** was determined according to the calibration curve given below using 1,3,5-trimethoxybenzene as the internal standard and as an average of three runs. In case of using (*R*)-**5a** the product *syn*-**5a** (82% yield, 7.5:1 d.r., >99% ee) was obtained, while the diastereomer *anti*-**3n** (47% yield, 15:1 d.r., >99% ee) was obtained when using (*S*)-**5a**. The enantiomeric excess of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) was determined using UPC^2 analysis on a Daicel Chiralpak IE-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/*i*-PrOH for 15 min; isocratic CO_2/ *i*-PrOH 60:40 for 8 min, gradient from 60:40 CO_2/*i*-PrOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 345 nm: *syn*-**5a**: τ = 19.3 min and *anti*-**5a**: τ = 21.2 min. The relative and absolute configurations were assigned by comparison with the crystal structure of **5k** (*Section F.2*).

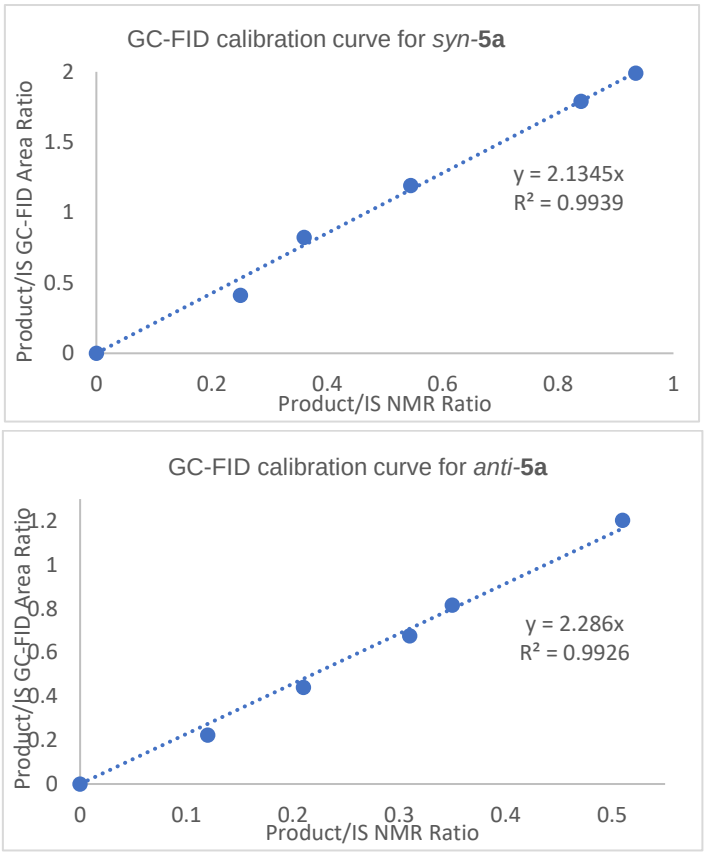
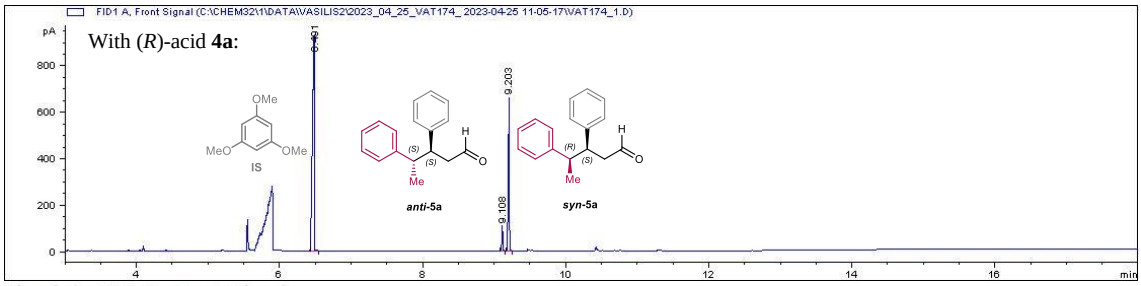
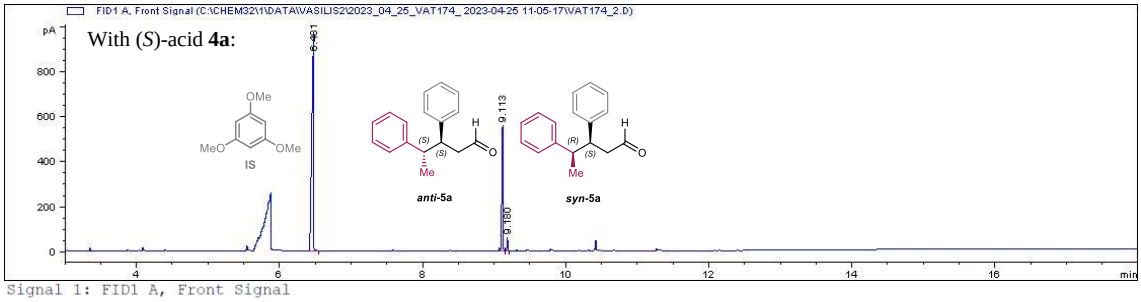


Figure S32. Calibration curves of compounds *syn*-**5a** and *anti*-**5a**. GC-FID calibration curves were obtained from 5mM solutions of the internal standard (IS = 1,3,5-trimethoxybenzene) in ethyl acetate with different concentrations of the corresponding product **5**.



Signal 1: FID1 A, Front Signal

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	6.491	BB	0.0241	1682.43994	921.91803	67.05925
2	9.108	BB	0.0140	94.66286	105.72913	3.77310
3	9.203	BB	0.0161	731.78290	660.01086	29.16765
Totals :				2508.88570	1687.65802	



Signal 1: FID1 A, Front Signal

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	6.481	BB	0.0254	1719.18945	956.05249	71.78216
2	9.113	BV	0.0163	627.41669	557.11401	26.19684
3	9.180	VB	0.0134	48.40331	55.51649	2.02101
Totals :				2395.00945	1568.68299	

Figure S33. GC-FID analysis to determine the conversion (analytical yield) of the enzymatic reaction.

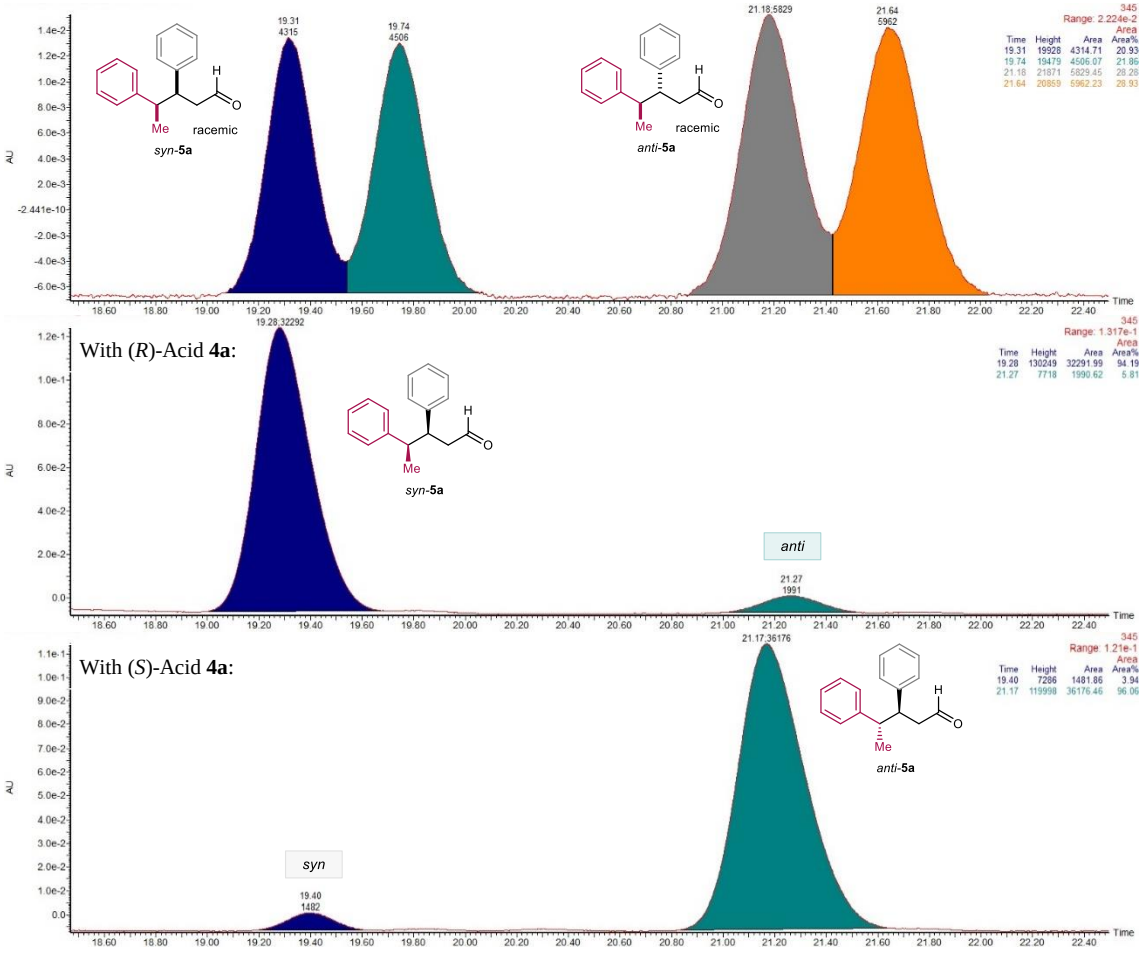
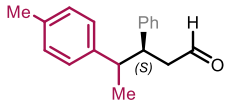


Figure S34. UPC^2 analysis to determine the ee of **5a** formed in the photobiocatalytic process.

(3*S*)-3-Phenyl-4-(*p*-tolyl)pentanal (5b)



syn- or *anti*-**5b**

Prepared according to **GP5**, using (*R*)- or (*S*)-2-(*p*-tolyl)propanoic acid **4b** (25 µL of a 87.5 mM stock solution in DMSO, 2.2 µmol) and cinnamaldehyde **1a** (25 µL of a 25 mM stock solution in DMSO, 0.68 µmol) as substrates in a 10% v/v DMSO/MOPS buffer pH 6.5 mixture. The crude extract was analyzed by GC-FID on HP-5 column. The analytical yield of product **5b** was determined according to the calibration curve given below using mesitylene as the internal standard and as an average of three runs. In case of using (*R*)-**4b** the product *syn*-**5b** (79% yield, 5.7:1 d.r., >99% ee) was obtained, while the diastereomer *anti*-**5b** (47% yield, 22:1 d.r., >99% ee) was obtained when using (*S*)-**5b**. The enantiomeric excess of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) was determined using UPC^2 analysis on a Daicel Chiralpak IA-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/EtOH for 11 min; isocratic 60:40 CO_2/EtOH for 6 min, gradient from 60:40 CO_2/EtOH to 100% CO_2 for 1 min, flow rate 1.0 mL/min, λ = 352 nm: *syn*-**5b**: τ = 16.5 min; *anti*-**5b**: τ = 14.3 min.

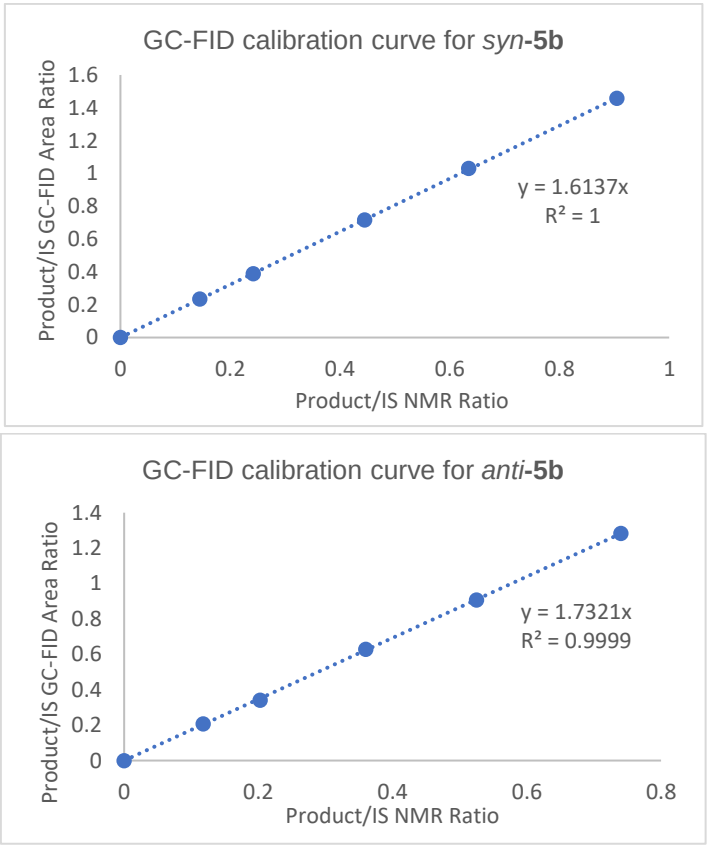
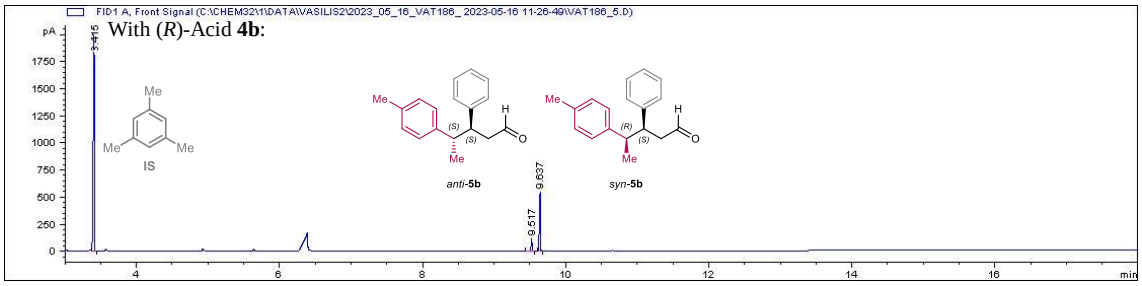
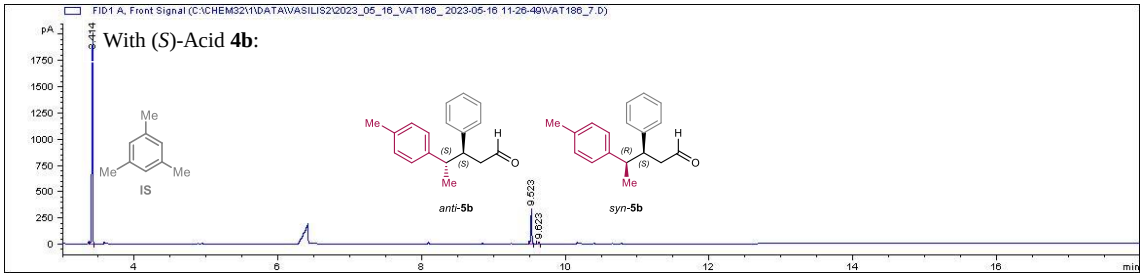


Figure S35. Calibration curves of compounds *syn*-**5b** and *anti*-**5b**. GC-FID calibration curves were obtained from 5mM solutions of the internal standard (IS = 1,3,5-trimethoxybenzene) in ethyl acetate with different concentrations of the corresponding product **5**.



Signal 1: FID1 A, Front Signal

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	3.415	VB	0.0168	2117.73584	1986.71289	76.56270
2	9.517	BB	0.0145	100.13588	111.06452	3.62022
3	9.637	BB	0.0150	548.14337	540.21558	19.81708
Totals :				2766.01509	2637.99299	



Signal 1: FID1 A, Front Signal

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	3.414	VB	0.0164	2109.98340	1978.31079	85.99857
2	9.523	BB	0.0165	329.73767	329.60760	13.43943
3	9.623	BB	0.0143	13.78869	15.62806	0.56200
Totals :				2453.50976	2323.54646	

Figure S36. GC-FID analysis to determine the conversion (analytical yield) of the enzymatic reaction.

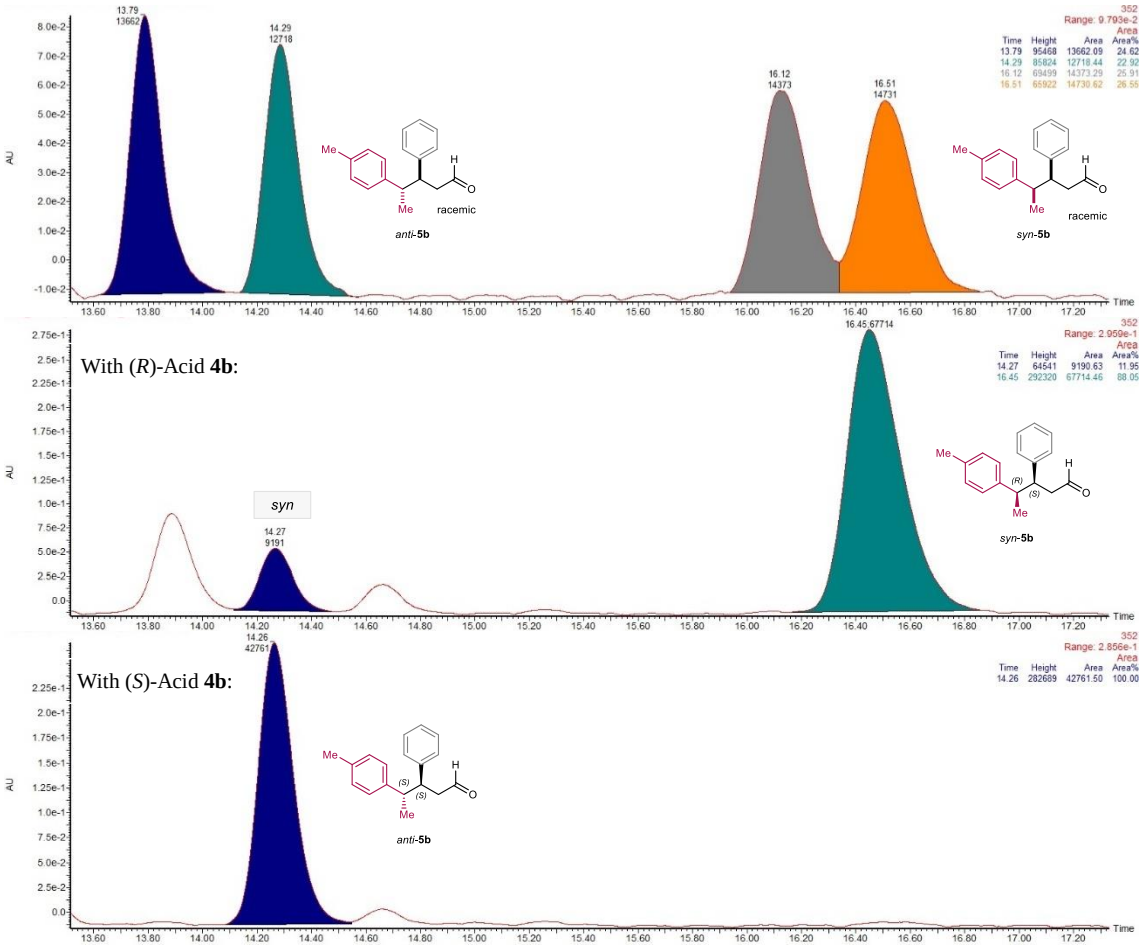
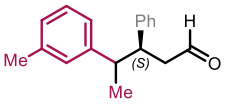


Figure S37. UPC^2 analysis to determine the ee of **5b** formed in the photobiocatalytic process.

(3*S*)-3-Phenyl-4-(*m*-tolyl)pentanal (5c)



syn- or *anti*-**5c**

Prepared according to **GP5**, using (*R*)- or (*S*)-2-(*m*-tolyl)propanoic acid **4c** (25 µL of a 87.5 mM stock solution in DMSO, 2.2 µmol) and cinnamaldehyde **1a** (25 µL of a 25 mM stock solution in DMSO, 0.68 µmol) as substrates in a 10% v/v DMSO/MOPS buffer pH 6.5 mixture. The crude extract was analyzed by GC-FID on HP-5 column. The analytical yield of product **5c** was determined according to the calibration curve given below using mesitylene as the internal standard and as an average of three runs. In case of using (*R*)-**4c** the product *syn*-**5c** (46% yield, 6:1 d.r., >99% ee) was obtained, while the diastereomer *anti*-**5c** (47% yield, 12.6:1 d.r., >99% ee) was obtained when using (*S*)-**4c**. The enantiomeric excess of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) was determined using UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/ EtOH for 13 min; isocratic 60:40 CO_2/EtOH for 2 min, gradient from 60:40 CO_2/EtOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 347 nm: *syn*-**5c**: τ = 10.0 min and *anti*-**5c**: τ = 10.7 min.

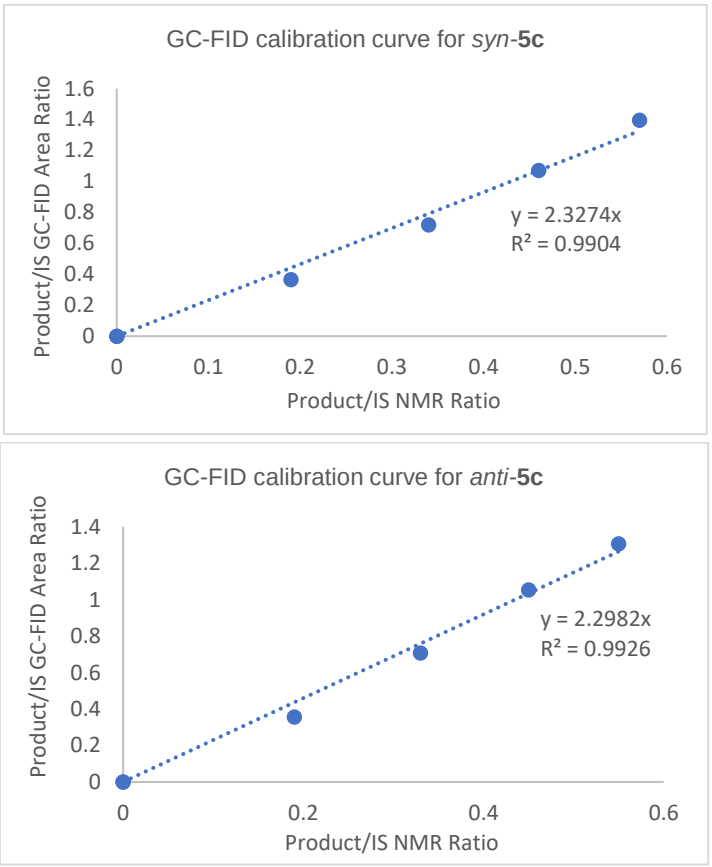
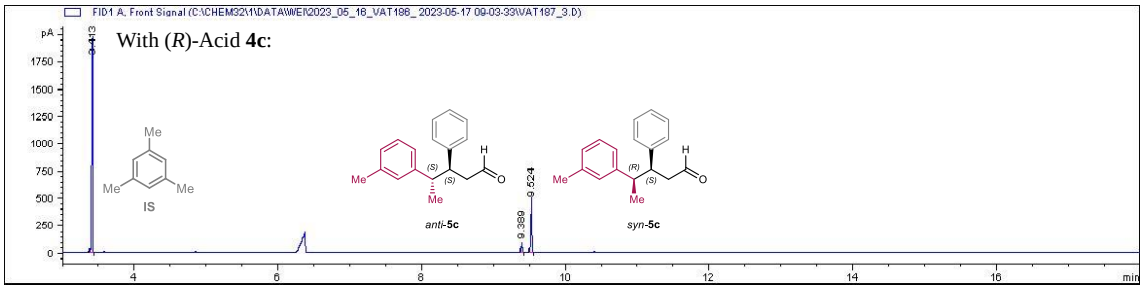
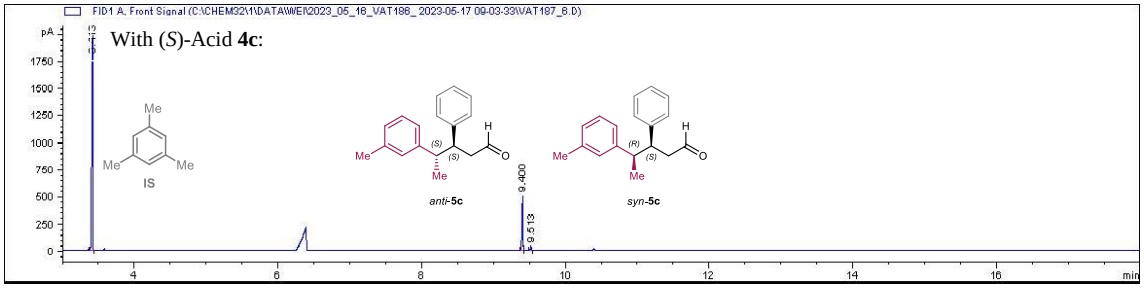


Figure S38. Calibration of compound *syn*-**5c** and *anti*-**5c**. GC-FID calibration curves were obtained from 5mM solutions of the internal standard (IS = 1,3,5-trimethoxybenzene) in ethyl acetate with different concentrations of the corresponding product **5**.



Signal 1: FID1 A, Front Signal

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	3.413	VB	0.0161	2112.70825	1906.20093	78.49244
2	9.389	BB	0.0133	81.17828	93.62732	3.01598
3	9.524	BB	0.0161	497.72070	479.91891	18.49158
Totals :				2691.60724	2479.74716	



Signal 1: FID1 A, Front Signal

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	3.413	VB	0.0170	2122.49097	1907.12451	79.45299
2	9.400	BB	0.0157	508.51978	507.04816	19.03585
3	9.513	BB	0.0141	40.36890	46.71998	1.51116
Totals :				2671.37965	2460.89265	

Figure S39. GC-FID analysis for determination of the conversion (analytical yield).

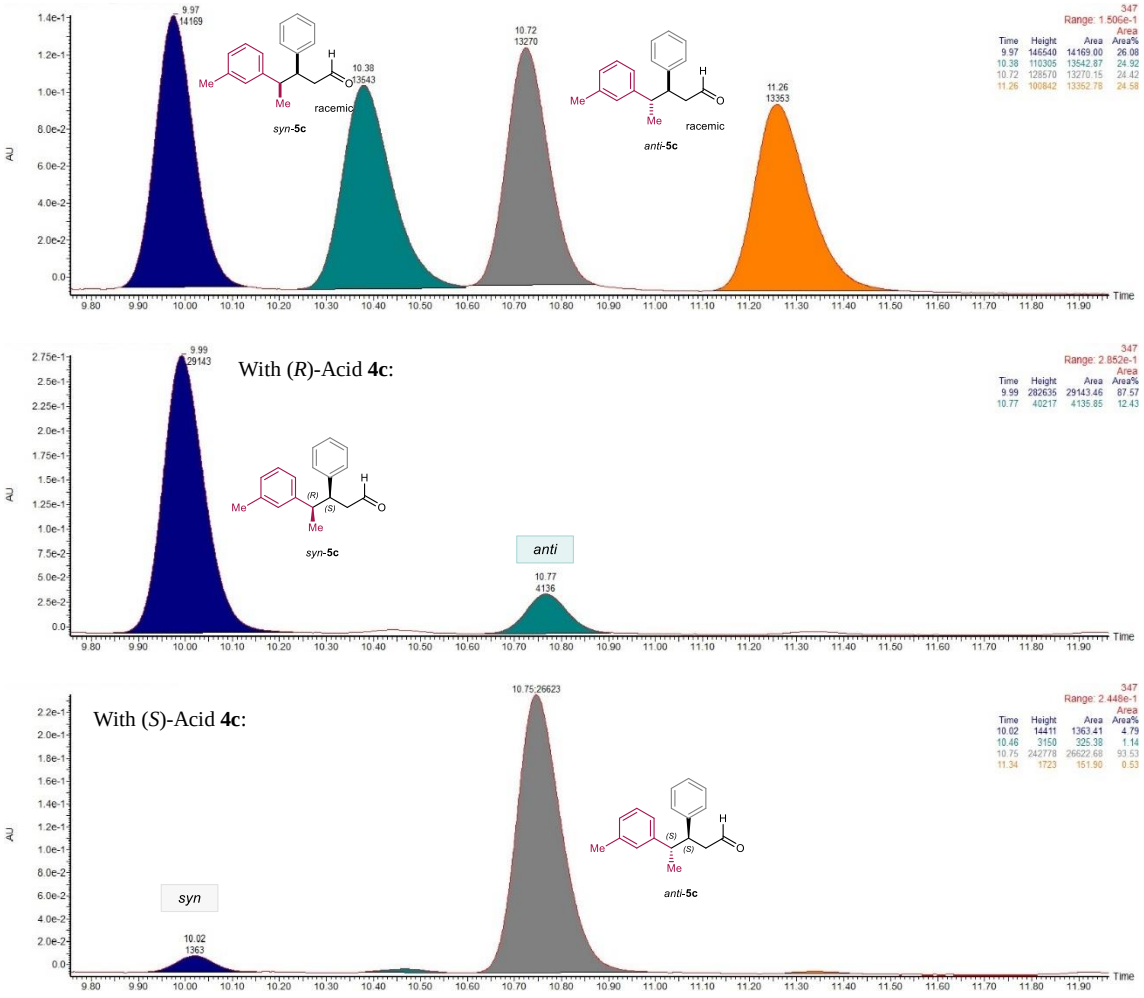
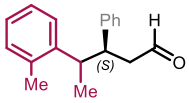


Figure S40. UPC^2 analysis to determine the ee of **5c** formed in the photobiocatalytic process.

(3*S*)-3-Phenyl-4-(*o*-tolyl)pentanal (5d)



syn- or *anti*-**5d**

Prepared according to **GP5**, using (*R*)- or (*S*)-2-(*o*-tolyl)propanoic acid **4d** (25 µL of a 87.5 mM stock solution in DMSO, 2.2 µmol) and cinnamaldehyde **1a** (25 µL of a 25 mM stock solution in DMSO, 0.68 µmol) as substrates in a 10% v/v DMSO/MOPS buffer pH 6.5 mixture. The crude extract was analyzed by GC-FID on HP-5 column. The analytical yield of product **5d** was determined according to the calibration curve given below using mesitylene as the internal standard and as an average of three runs. In case of using (*R*)-**4d** the product *syn*-**5d** (38% yield, 4.9:1 d.r., 94% ee) was obtained, while the diastereomer *anti*-**5d** (35% yield, 6.7:1 d.r., 99% ee) was obtained when using (*S*)-**4d**. The enantiomeric excess of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) was determined using UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/ MeOH for 13 min; isocratic 60:40 CO_2/MeOH for 2 min, gradient from 60:40 CO_2/MeOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 350 nm: *syn*-**5d**: τ = 9.6 min and *anti*-**5d**: τ = 10.4 min.

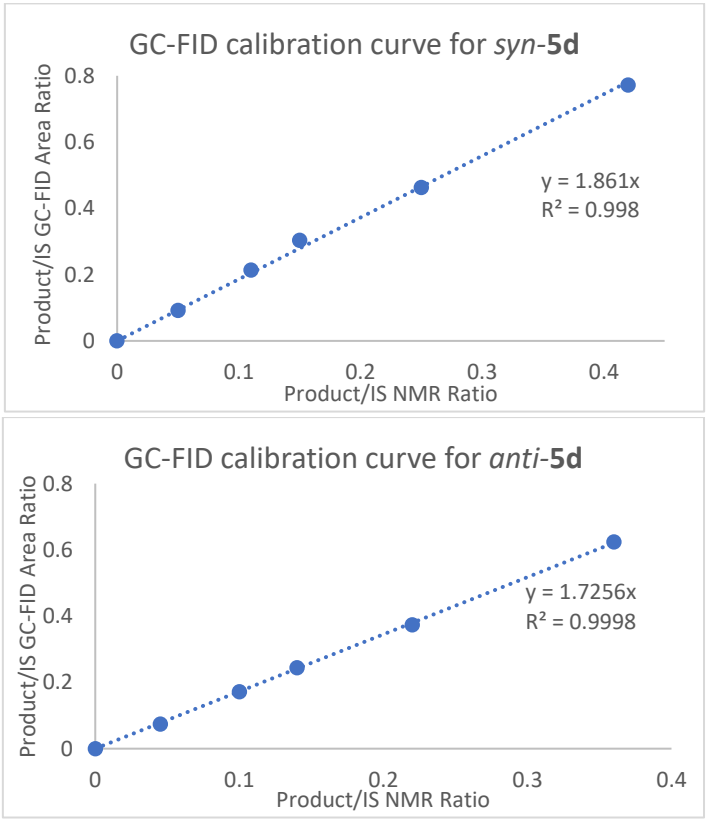
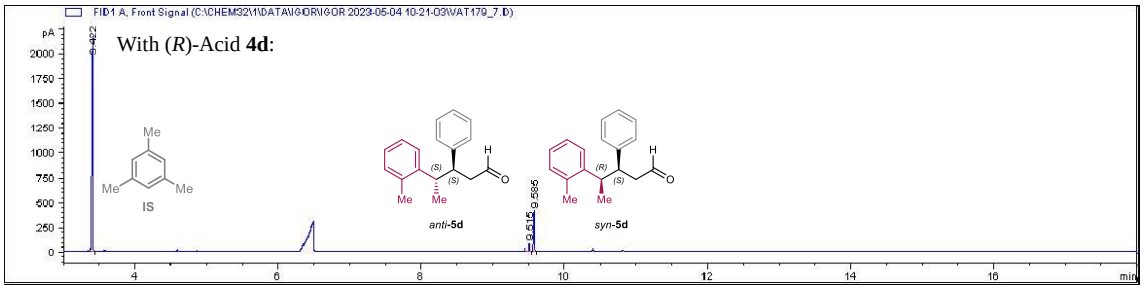
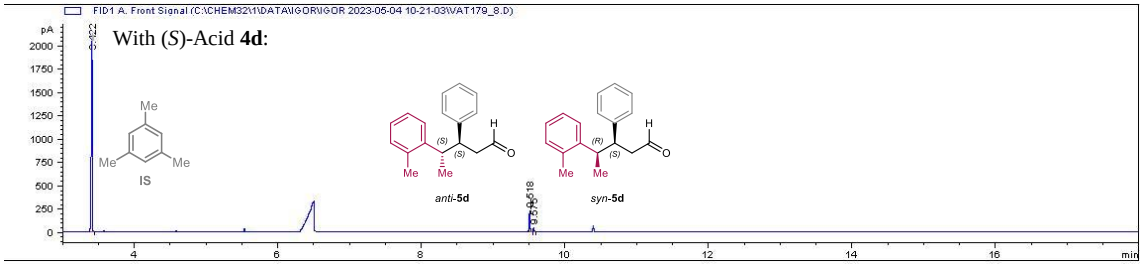


Figure S41. Calibration curve of compounds *syn*-**5d** and *anti*-**5d**. GC-FID calibration curves were obtained from 5mM solutions of the internal standard (IS = 1,3,5-trimethoxybenzene) in ethyl acetate with different concentrations of the corresponding product **5**.



Signal 1: FID1 A, Front Signal

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	3.422	VB	0.0171	2402.41040	2140.72632	83.22842
2	9.515	BB	0.0150	75.28152	79.52168	2.60803
3	9.585	BB	0.0165	408.83444	407.65677	14.16354
Totals :				2886.52637	2627.90477	



Signal 1: FID1 A, Front Signal

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	3.422	VB	0.0177	2376.56274	2144.33398	90.38606
2	9.518	BB	0.0158	216.87907	229.10233	8.24840
3	9.575	BB	0.0139	35.90475	42.25375	1.36554
Totals :				2629.34657	2415.69006	

Figure S42. GC-FID analysis for determination of the conversion (analytical yield).

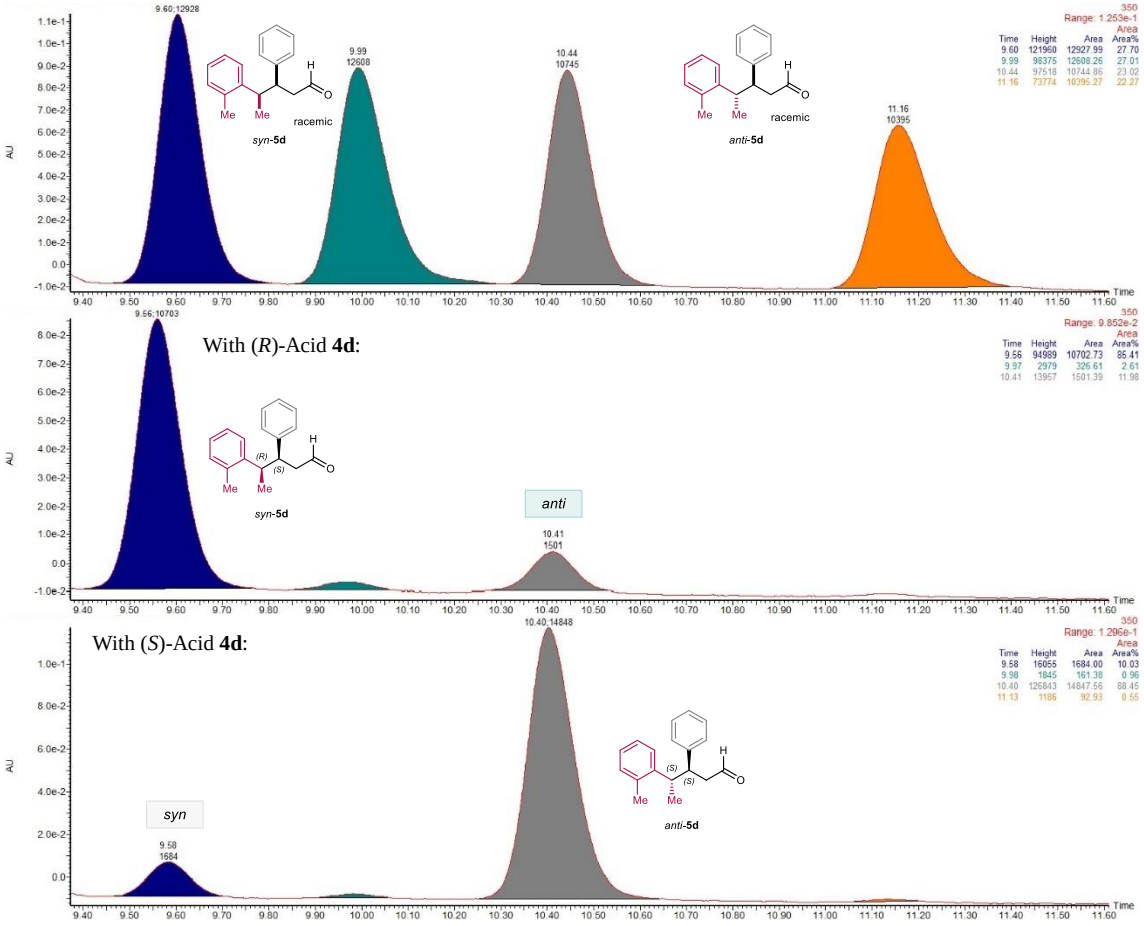
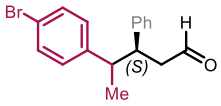


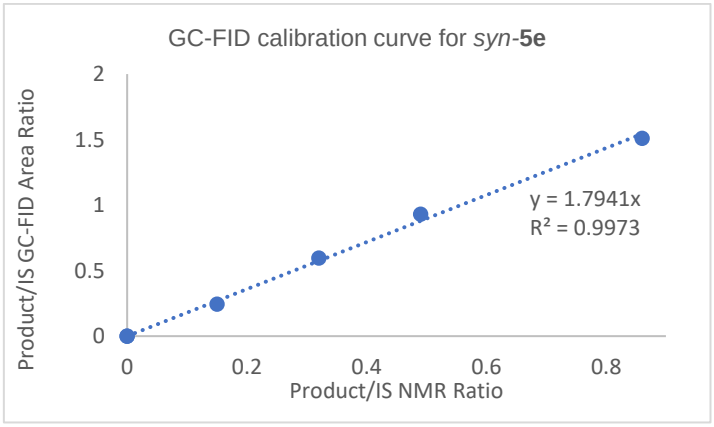
Figure S43. UPC^2 analysis to determine the ee of **5d** formed in the photobiocatalytic process.

(3*S*)-4-(4-Bromophenyl)-3-phenylpentanal (5e)



syn- or *anti*-**5e**

Prepared according to **GP5**, using (*R*)- or (*S*)-2-(4-bromophenyl)propionic acid **4e** (25 µL of a 87.5 mM stock solution in DMSO, 2.2 µmol) and cinnamaldehyde **1a** (25 µL of a 25 mM stock solution in DMSO, 0.68 µmol) as substrates in a 10% v/v DMSO/MOPS buffer pH 6.5 mixture. The crude extract was analyzed by GC-FID on HP-5 column. The analytical yield of product **5e** was determined according to the calibration curve given below using mesitylene as the internal standard and as an average of three runs. In case of using (*R*)-**4e** the product *syn*-**5e** (54% yield, 5.8:1 d.r., 90 % ee) was obtained, while the diastereomer *anti*-**5e** (50% yield, 7.8:1 d.r., 96% ee) was obtained when using (*S*)-**4e**. The enantiomeric excess of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) was determined using UPC^2 analysis on a Daicel Chiralpak IB-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 85:15 CO_2/*i*-PrOH for 37 min; isocratic 85:15 CO_2/*i*-PrOH for 26 min, gradient from 85:15 CO_2/*i*-PrOH to 100% CO_2 for 1 min, flow rate 1.0 mL/min, λ = 344 nm: *syn*-**5e**: τ = 54.9 min and *anti*-**5e**: τ = 58.8 min.



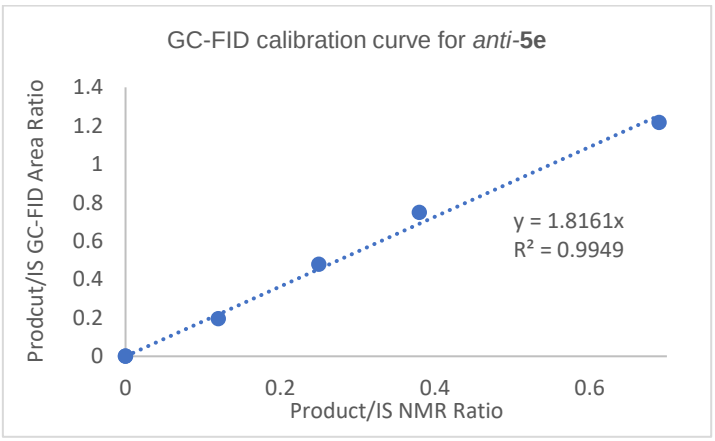
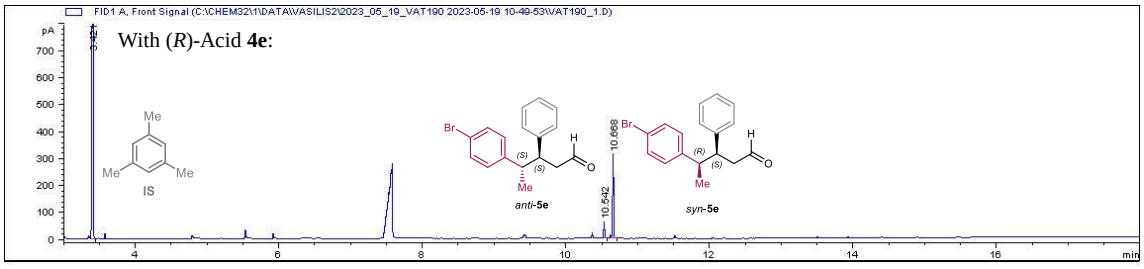
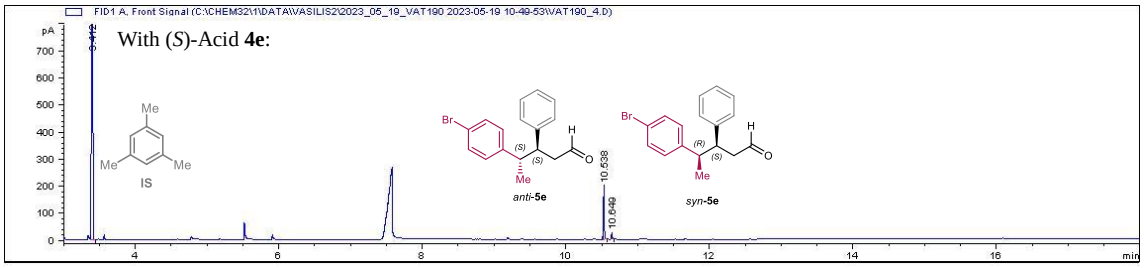


Figure S44. Calibration curves of compounds *syn*-**5e** and *anti*-**5e**. GC-FID calibration curves were obtained from 5mM solutions of the internal standard (IS = 1,3,5-trimethoxybenzene) in ethyl acetate with different concentrations of the corresponding product **5**..



Signal 1: FID1 A, Front Signal

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	3.421	VB	0.0179	2136.38086	1898.52722	84.93313
2	10.542	BB	0.0140	55.76238	60.10532	2.21687
3	10.668	BB	0.0170	323.22485	310.05899	12.85000
Totals :				2515.36809	2268.69154	



Signal 1: FID1 A, Front Signal

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	3.412	VB	0.0159	2112.55225	1941.07397	91.59583
2	10.538	BB	0.0136	173.92023	195.32001	7.54082
3	10.649	BB	0.0145	19.91230	22.08399	0.86336
Totals :				2306.38478	2158.47797	

Figure S45. GC-FID analysis for determination of the conversion (analytical yield)

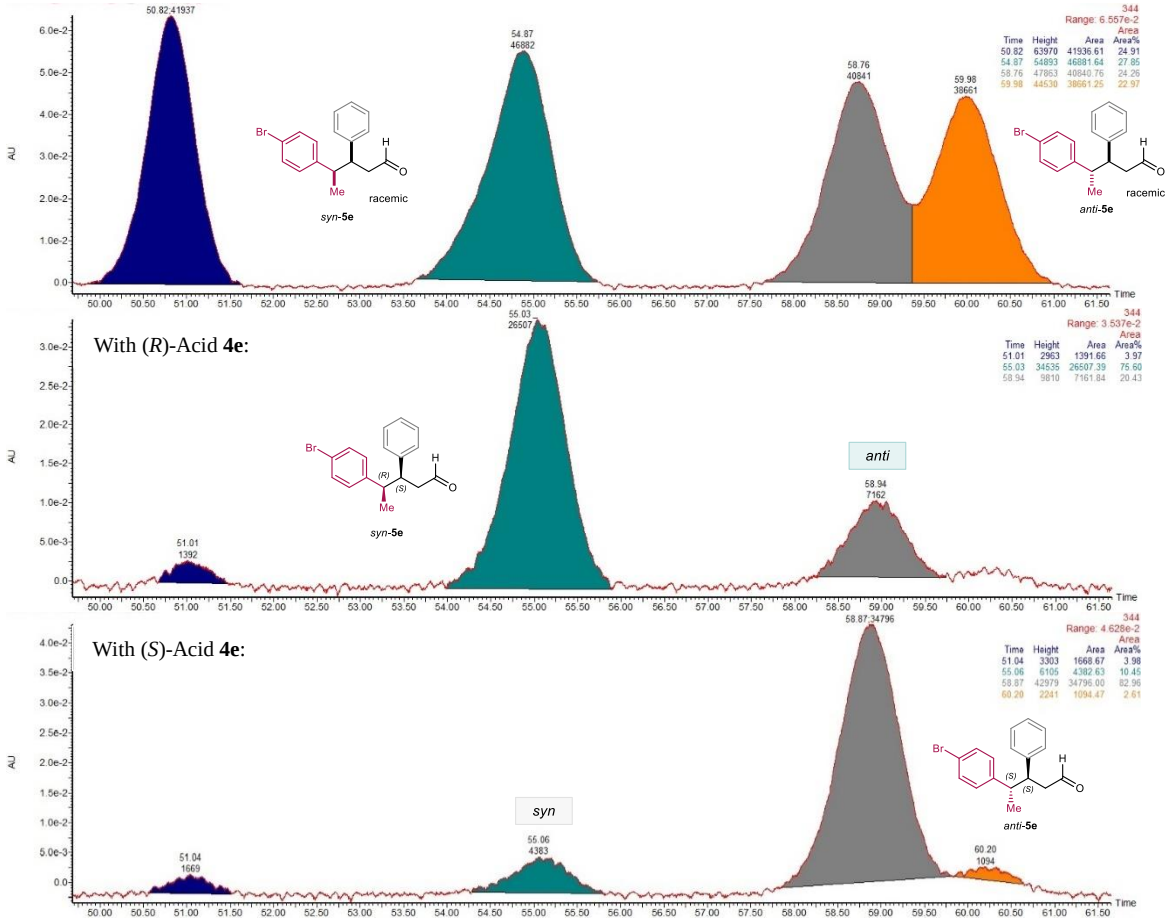
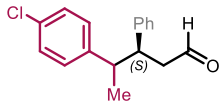


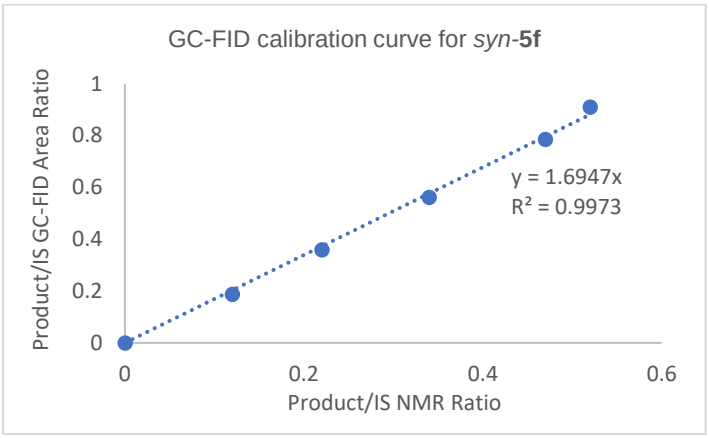
Figure S46. UPC^2 analysis to determine the ee of **5e** formed in the photobiocatalytic process.

(3*S*)-4-(4-Chlorophenyl)-3-phenylpentanal (5f)



syn- or *anti*-**5f**

Prepared according to **GP5**, using (*R*)- or (*S*)-2-(4-chlorophenyl)propionic acid **4f** (25 µL of a 87.5 mM stock solution in DMSO, 2.2 µmol) and cinnamaldehyde **1a** (25 µL of a 25 mM stock solution in DMSO, 0.68 µmol) as substrates in a 10% v/v DMSO/MOPS buffer pH 6.5 mixture. The crude extract was analyzed by GC-FID on HP-5 column. The analytical yield of product **5f** was determined according to the calibration curve given below using mesitylene as the internal standard and as an average of three runs. In case of using (*R*)-**4f** the product *syn*-**5f** (55% yield, 6.1:1 d.r., 98% ee) was obtained, while the diastereomer *anti*-**5f** (42% yield, 16:1 d.r., 98% ee) was obtained when using (*S*)-**4f**. The enantiomeric excess of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) was determined using UPC^2 analysis on a Daicel Chiralpak IE-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/ EtOH for 21 min; isocratic 60:40 CO_2/EtOH for 6 min, gradient from 60:40 CO_2/EtOH to 100% CO_2 for 1 min, flow rate: 1.0 mL/min, λ = 350 nm: *syn*-**5f:** τ = 22.1 min and *anti*-**5f**: τ = 23.2 min.



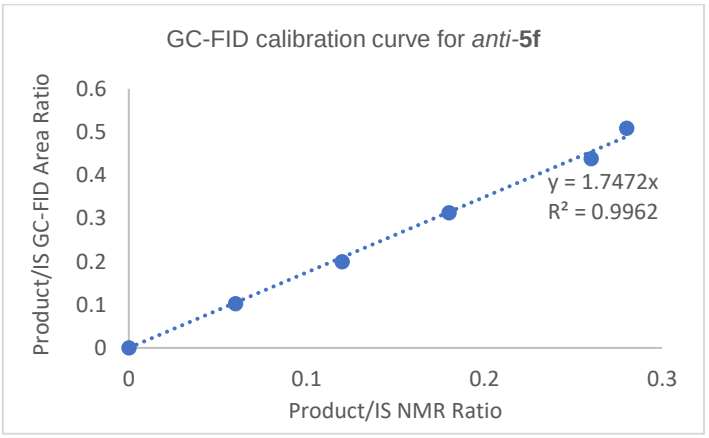
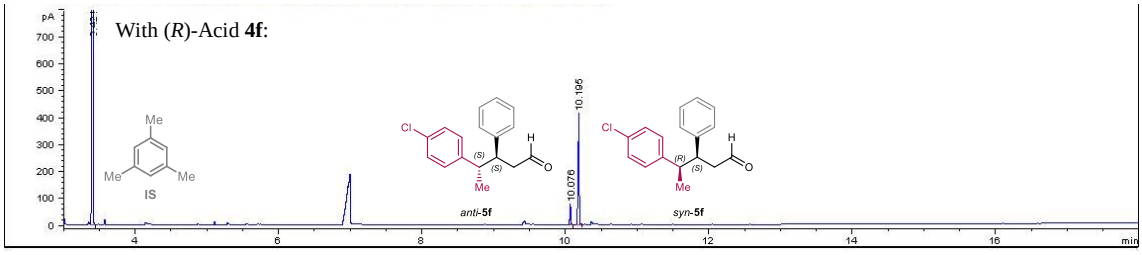


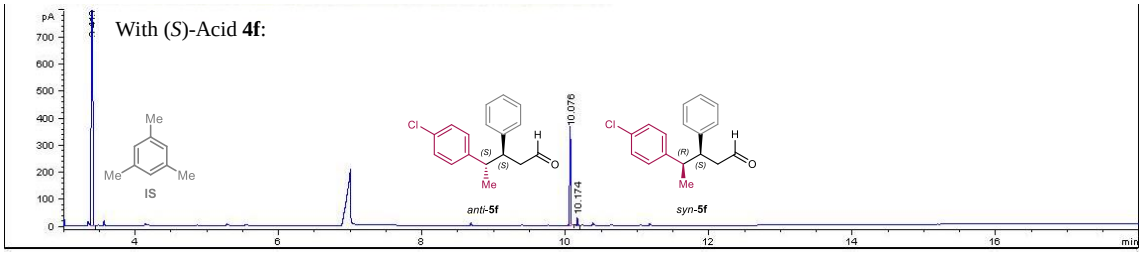
Figure S47. Calibration curves of compounds *syn*-**5f** and *anti*-**5f**. GC-FID calibration curves were obtained from 5mM solutions of the internal standard (IS = 1,3,5-trimethoxybenzene) in ethyl acetate with different concentrations of the corresponding product **5**.



Signal 1: FID1 A, Front Signal

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	3.421	VB	0.0181	2267.84009	1987.21375	81.60543
2	10.076	BB	0.0153	70.48174	73.02837	2.53620
3	10.195	BB	0.0173	440.70917	410.59814	15.85838

Totals : 2779.03099 2470.84026



Signal 1: FID1 A, Front Signal

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	3.413	VB	0.0163	2272.03271	2018.44507	85.56831
2	10.076	BB	0.0159	360.39618	352.52725	13.57309
3	10.174	BB	0.0131	22.79782	26.81590	0.85860

Totals : 2655.22671 2397.78822

Figure S48. GC-FID analysis for determination of the conversion (analytical yield)

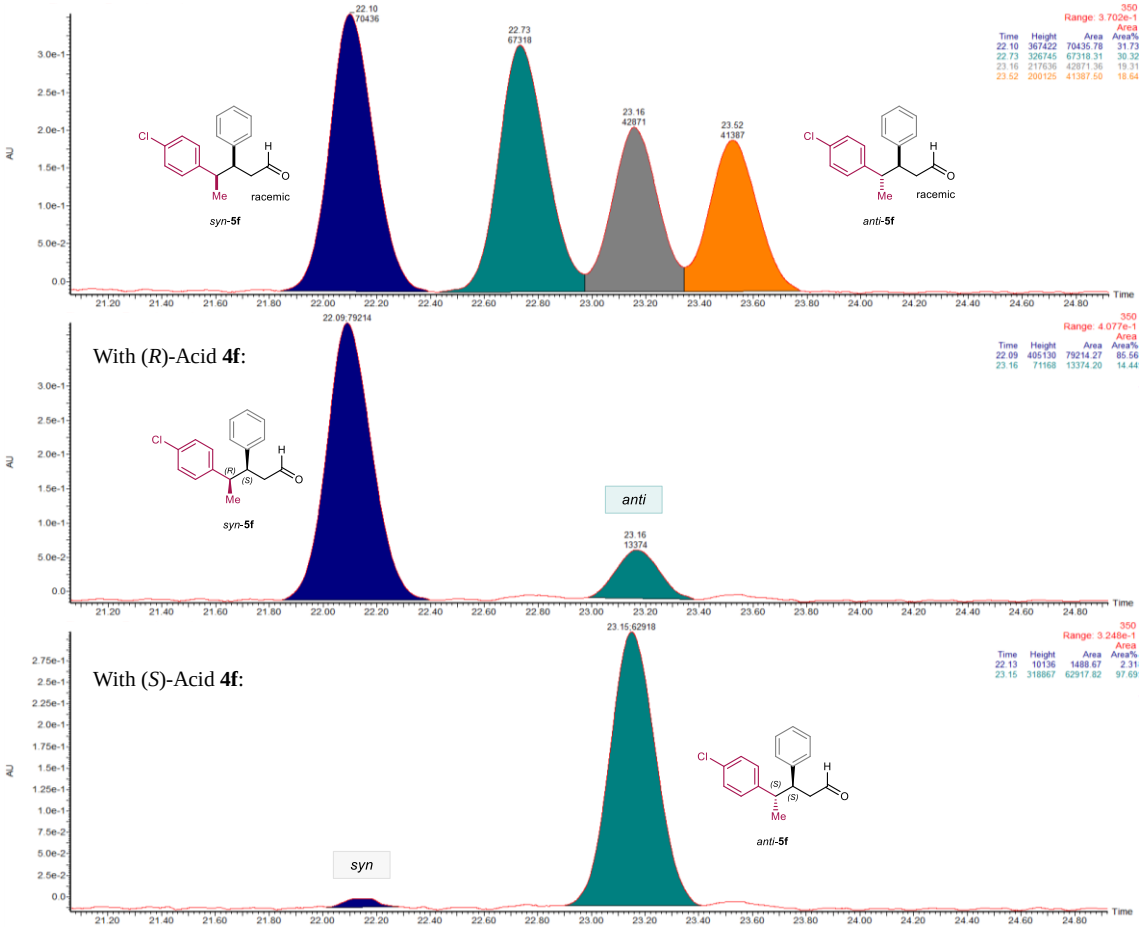
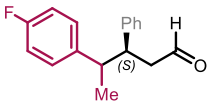


Figure S49. UPC^2 analysis to determine the ee of **5f** formed in the photobiocatalytic process.

(3*S*)-4-(4-Fluorophenyl)-3-phenylpentanal (5g)



syn- or *anti*-**5g**

Prepared according to **GP5**, using (*R*)- or (*S*)-2-(4-fluorophenyl)propionic acid **4g** (25 µL of a 87.5 mM stock solution in DMSO, 2.2 µmol) and cinnamaldehyde **1a** (25 µL of a 25 mM stock solution in DMSO, 0.68 µmol) as substrates in a 10% v/v DMSO/MOPS buffer pH 6.5 mixture. The crude extract was analyzed by GC-FID on HP-5 column. The analytical yield of product **5g** was determined according to the calibration curve given below using mesitylene as the internal standard and as an average of three runs. In case of using (*R*)-**4g** the product *syn*-**5g** (54% yield, 6.5:1 d.r., 98% ee) was obtained, while the diastereomer *anti*-**5g** (40% yield, 12.3:1 d.r., 96% ee) was obtained when using (*S*)-**4g**. The enantiomeric excess of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) was determined using UPC^2 analysis on a Daicel Chiralpak IE-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 70:30 CO_2/ EtOH for 9 min; isocratic70:30 CO_2/EtOH for 4 min, gradient from 70:30 CO_2/EtOH to 100% CO_2 for 1 min, flow rate: 2.0 mL/min, λ = 347 nm: *syn*-**5g**: τ = 10.7 min and *anti*-**5g**: τ = 11.3 min.

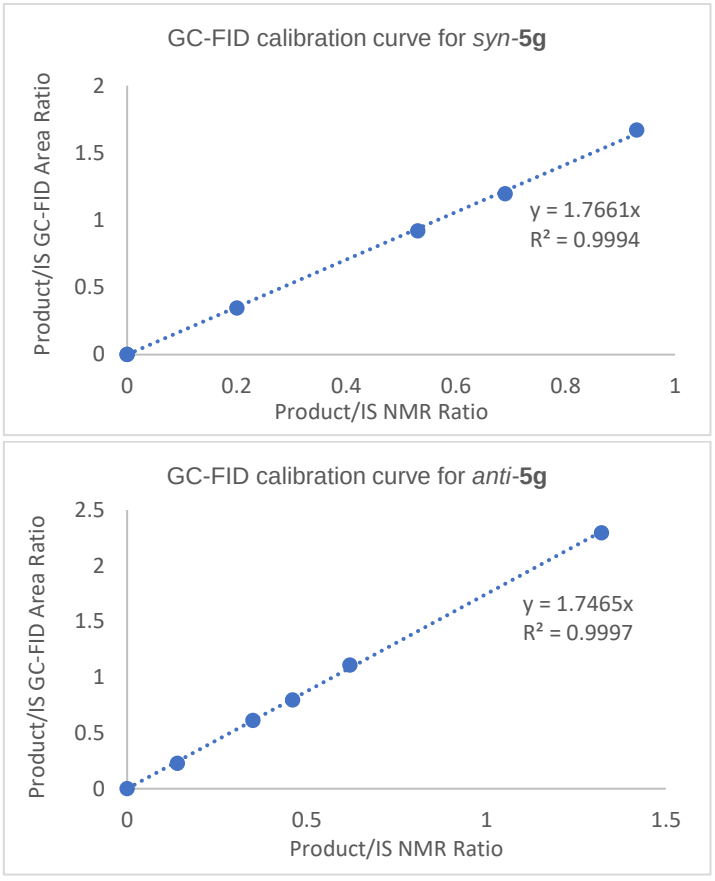
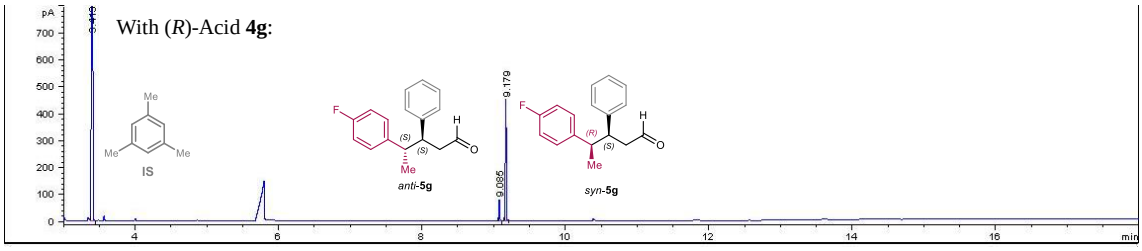


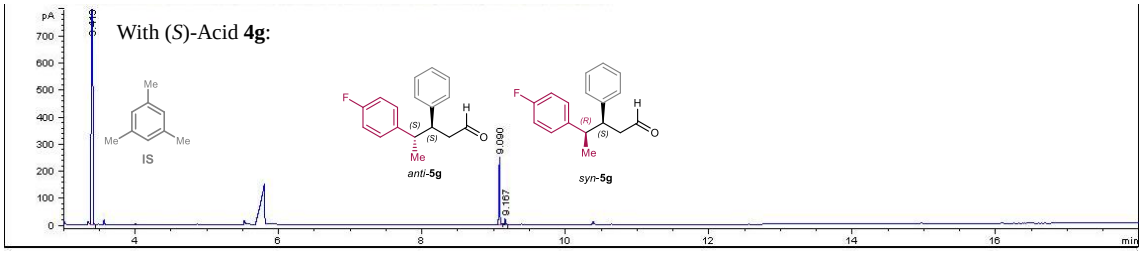
Figure S50. Calibration curves of compounds *syn*-**5g** and *anti*-**5g**. GC-FID calibration curves were obtained from 5mM solutions of the internal standard (IS = 1,3,5-trimethoxybenzene) in ethyl acetate with different concentrations of the corresponding product **5**.



Signal 1: FID1 A, Front Signal

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	3.413	VB	0.0172	2275.17773	2014.85156	81.55266
2	9.085	BB	0.0138	68.23605	75.23151	2.44589
3	9.179	BB	0.0157	446.41278	445.52637	16.00145

Totals : 2789.82657 2535.60944



Signal 1: FID1 A, Front Signal

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	3.413	VB	0.0172	2246.75244	1982.29211	89.99223
2	9.090	BB	0.0149	230.75433	246.52335	9.24272
3	9.167	BB	0.0149	19.10050	20.50083	0.76506

Totals : 2496.60728 2249.31629

Figure S51. GC-FID analysis for determination of the conversion (analytical yield)

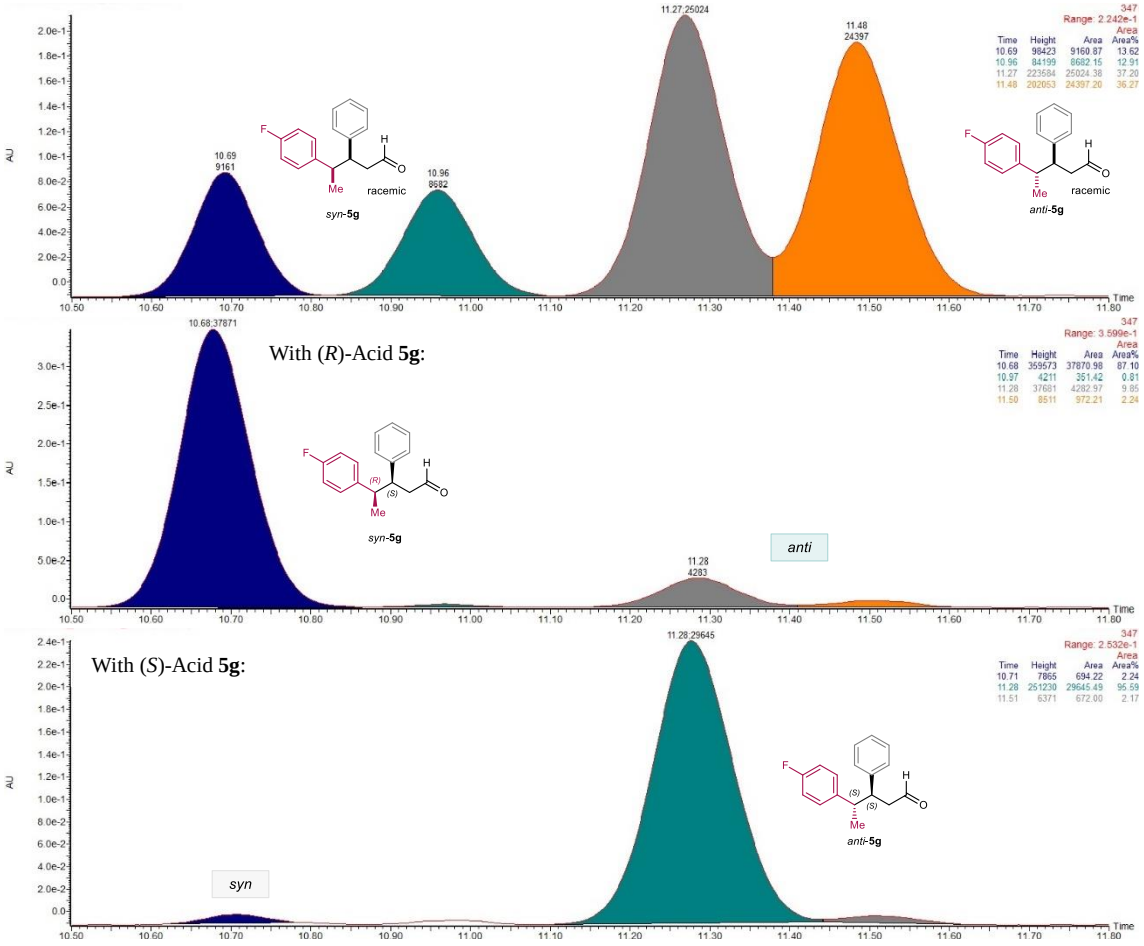
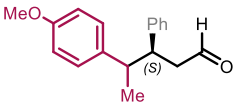


Figure S52. UPC^2 analysis to determine the ee of **5g** formed in the photobiocatalytic process.

(3*S*)-4-(4-Methoxyphenyl)-3-phenylpentanal (5h)



syn- or *anti*-**5h**

Prepared according to **GP5**, using (*R*)- or (*S*)-2-(4-methoxyphenyl)propionic acid **4h** (25 µL of a 87.5 mM stock solution in DMSO, 2.2 µmol) and cinnamaldehyde **1a** (25 µL of a 25 mM stock solution in DMSO, 0.68 µmol) as substrates in a 10% v/v DMSO/MOPS buffer pH 6.5 mixture. The crude extract was analyzed by GC-FID on HP-5 column. The analytical yield of product **5h** was determined according to the calibration curve given below using mesitylene as the internal standard and as an average of three runs. In case of using (*R*)-**4h** the product *syn*-**5h** (54% yield, 3.2:1 d.r., >99% ee) was obtained, while the diastereomer *anti*-**5h** (43% yield, 6.7:1 d.r., >99% ee) was obtained when using (*S*)-**4h**. The enantiomeric excess of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) was determined using UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 70:30 CO_2/EtOH for 21 min; isocratic 70:30 CO_2/EtOH for 6 min, gradient from 70:30 CO_2/EtOH to 100% CO_2 for 2 min, flow rate 1.0 mL/min, λ = 346 nm: *syn*-**5h**: τ = 20.0 min and *anti*-**5h**: τ = 21.1 min.

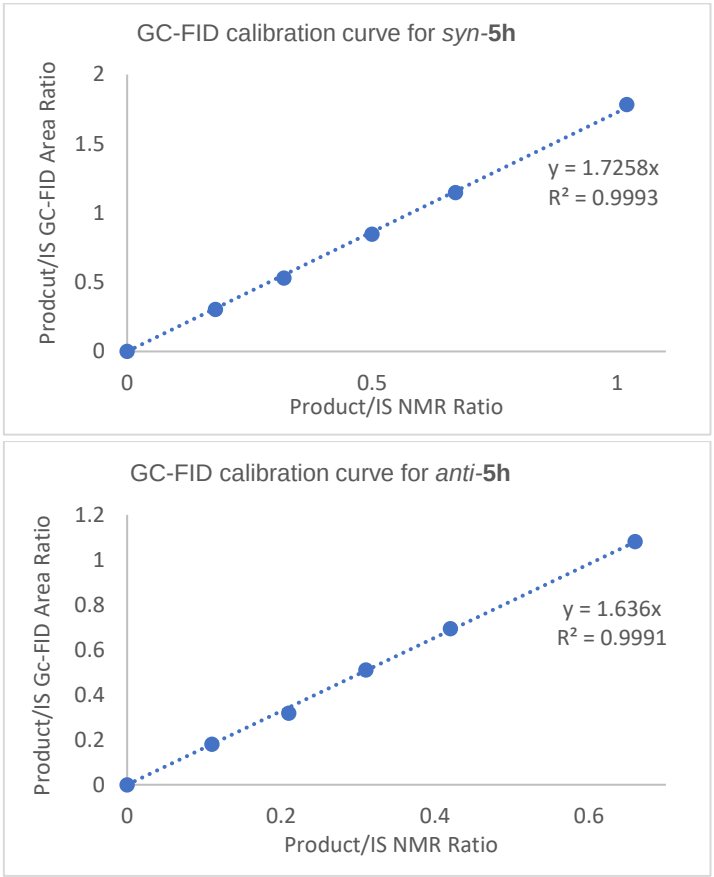
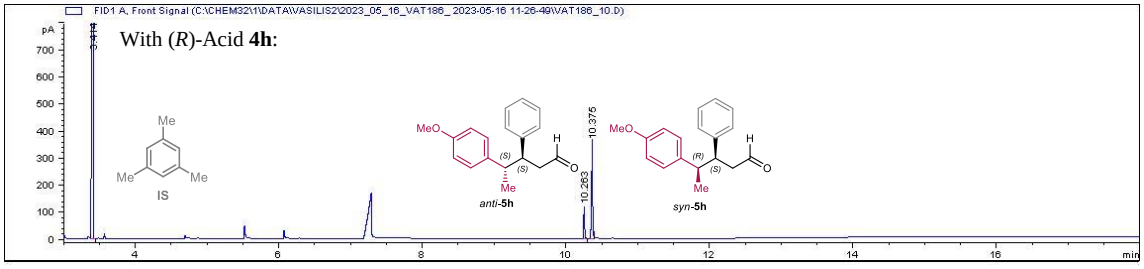


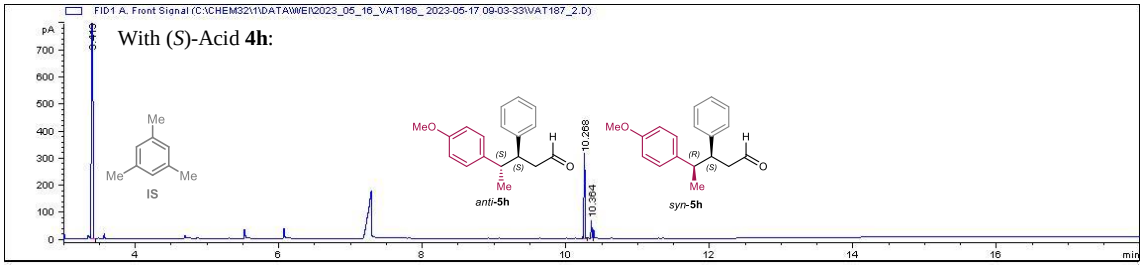
Figure S53. Calibration curves of compounds *syn*-**5h** and *anti*-**5h**. GC-FID calibration curves were obtained from 5mM solutions of the internal standard (IS = 1,3,5-trimethoxybenzene) in ethyl acetate with different concentrations of the corresponding product **5**.



Signal 1: FID1 A, Front Signal

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	3.414	VB	0.0175	2116.52783	1950.99268	81.57850
2	10.263	BB	0.0149	108.06819	115.56167	4.16533
3	10.375	BV	0.0153	369.87152	355.36548	14.25616

Totals : 2594.46754 2421.91982



Signal 1: FID1 A, Front Signal

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	3.413	VB	0.0159	2122.66724	1956.96423	85.23711
2	10.268	BB	0.0159	313.26407	306.86844	12.57933
3	10.364	BV	0.0134	54.37756	62.40805	2.18357

Totals : 2490.30886 2326.24072

Figure S54. GC-FID analysis for determination of the conversion (analytical yield)

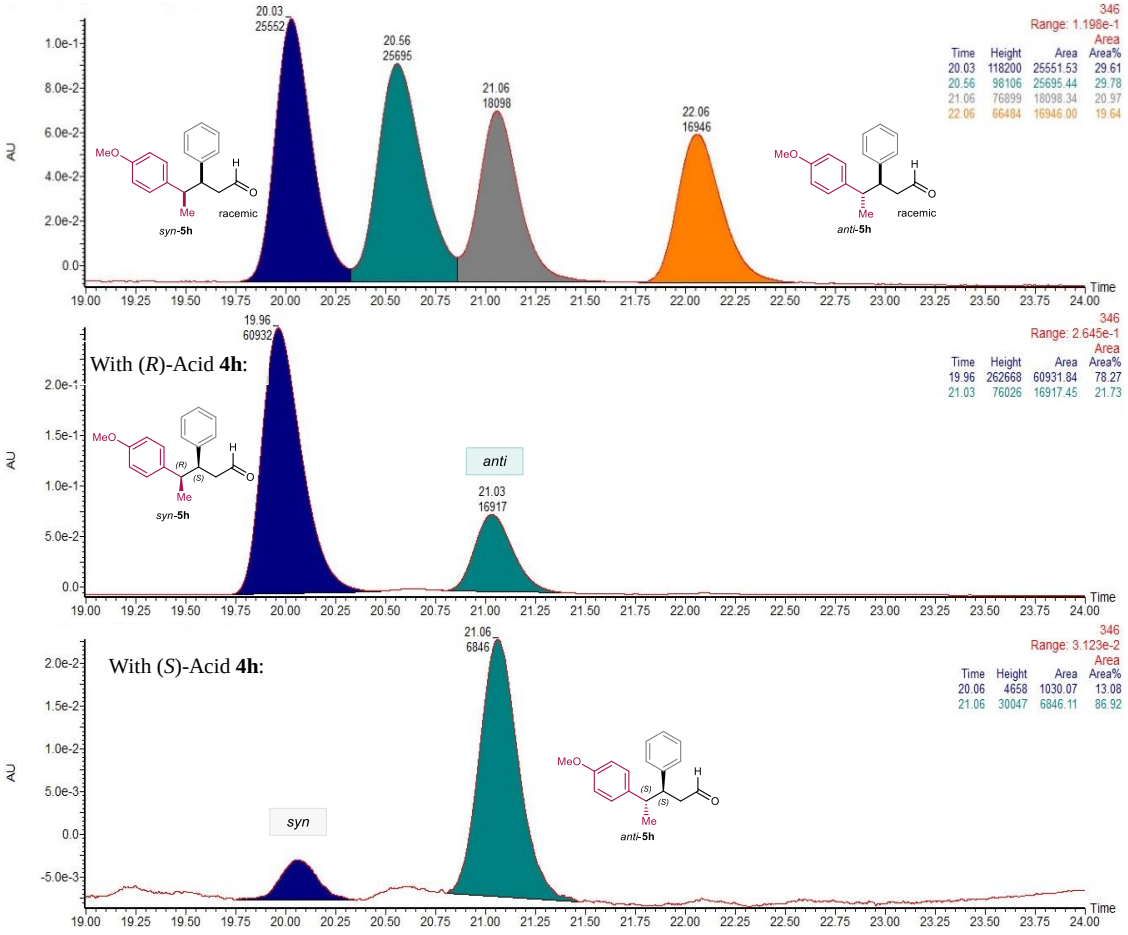
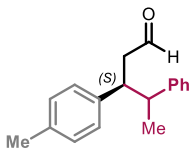


Figure S55. UPC^2 analysis to determine the ee of **5h** formed in the photobiocatalytic process.

(3*S*)-4-Phenyl-3-(p-tolyl)pentanal (5i)



syn- or *anti*-**5i**

Prepared according to **GP5**, using (*R*)- or (*S*)-2-phenylpropionic acid **4a** (25 µL of a 87.5 mM stock solution in DMSO, 2.2 µmol) and enal **1b** (25 µL of a 25 mM stock solution in DMSO, 0.68 µmol) as substrates in a 10% v/v DMSO/MOPS buffer pH 6.5 mixture. The crude extract was analyzed by GC-FID on HP-5 column. The analytical yield of product **5i** was determined according to the calibration curve given below using mesitylene as the internal standard and as an average of three runs. In case of using (*R*)-**4a** the product *syn*-**5i** (65% yield, 7.7:1 d.r., >99% ee) was obtained, while the diastereomer *anti*-**5i** (37% yield, 13.8:1 d.r., >99% ee) was obtained when using (*S*)-**4a**. The enantiomeric excess of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) was determined using UPC^2 analysis on a Daicel Chiralpak IE-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/MeOH for 14 min; isocratic 60:40 CO_2/EtOH for 4 min, gradient from 60:40 CO_2/EtOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 353 nm: *syn*-**5i**: τ = 13.5 min and *anti*-**5i**: τ = 14.4 min.

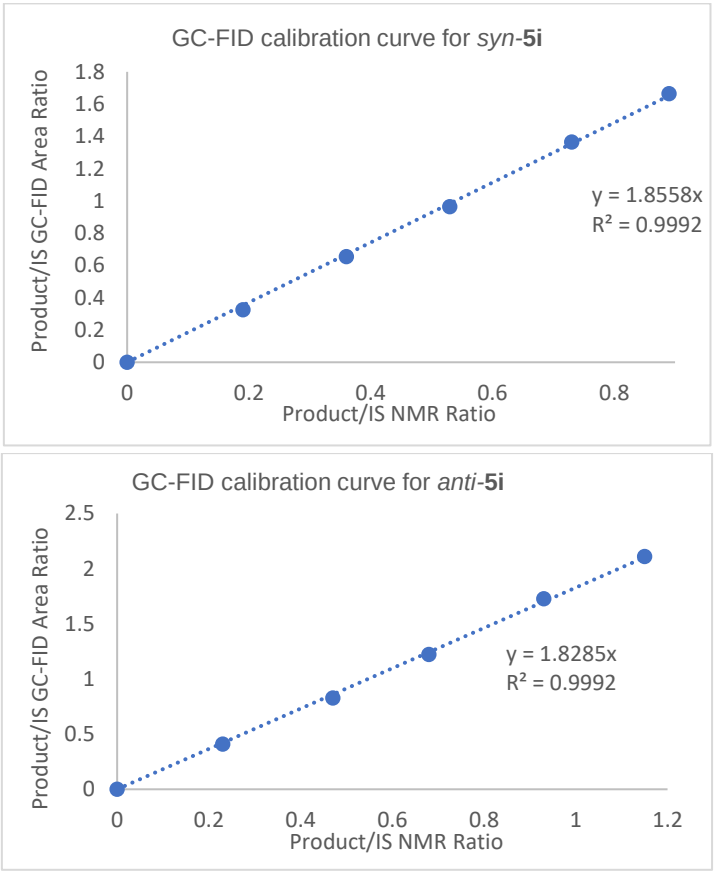
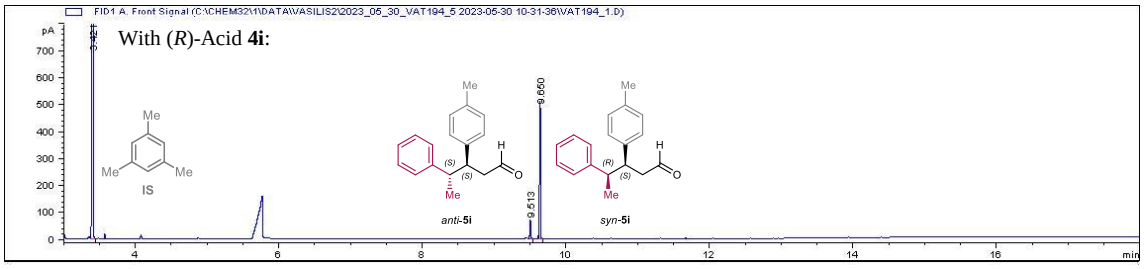


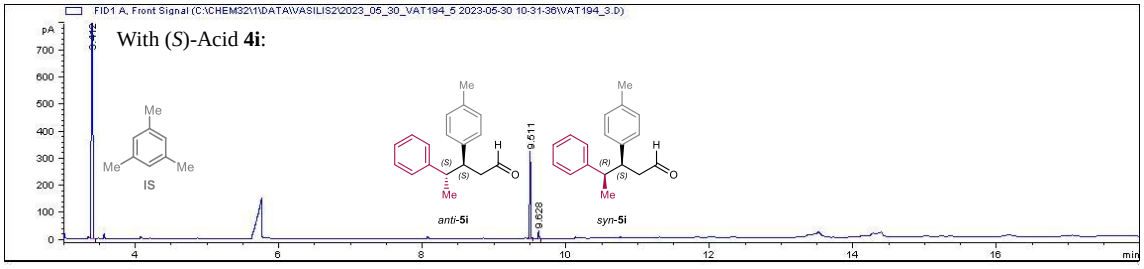
Figure S56. Calibration curves of compounds *syn*-**5i** and *anti*-**5i**. GC-FID calibration curves were obtained from 5mM solutions of the internal standard (IS = 1,3,5-trimethoxybenzene) in ethyl acetate with different concentrations of the corresponding product **5**.



Signal 1: FID1 A, Front Signal

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	3.421	VB	0.0180	2240.30444	1984.93481	79.51419
2	9.513	BB	0.0150	62.46993	66.29132	2.21722
3	9.650	BB	0.0163	514.71588	487.91730	18.26859

Totals : 2817.49025 2539.14343



Signal 1: FID1 A, Front Signal

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	3.412	VB	0.0169	2205.32642	1992.02087	86.82277
2	9.511	BB	0.0154	311.83420	319.31412	12.27678
3	9.628	BB	0.0144	22.87184	25.65618	0.90045

Totals : 2540.03246 2336.99117

Figure S57. GC-FID analysis for determination of the conversion (analytical yield)

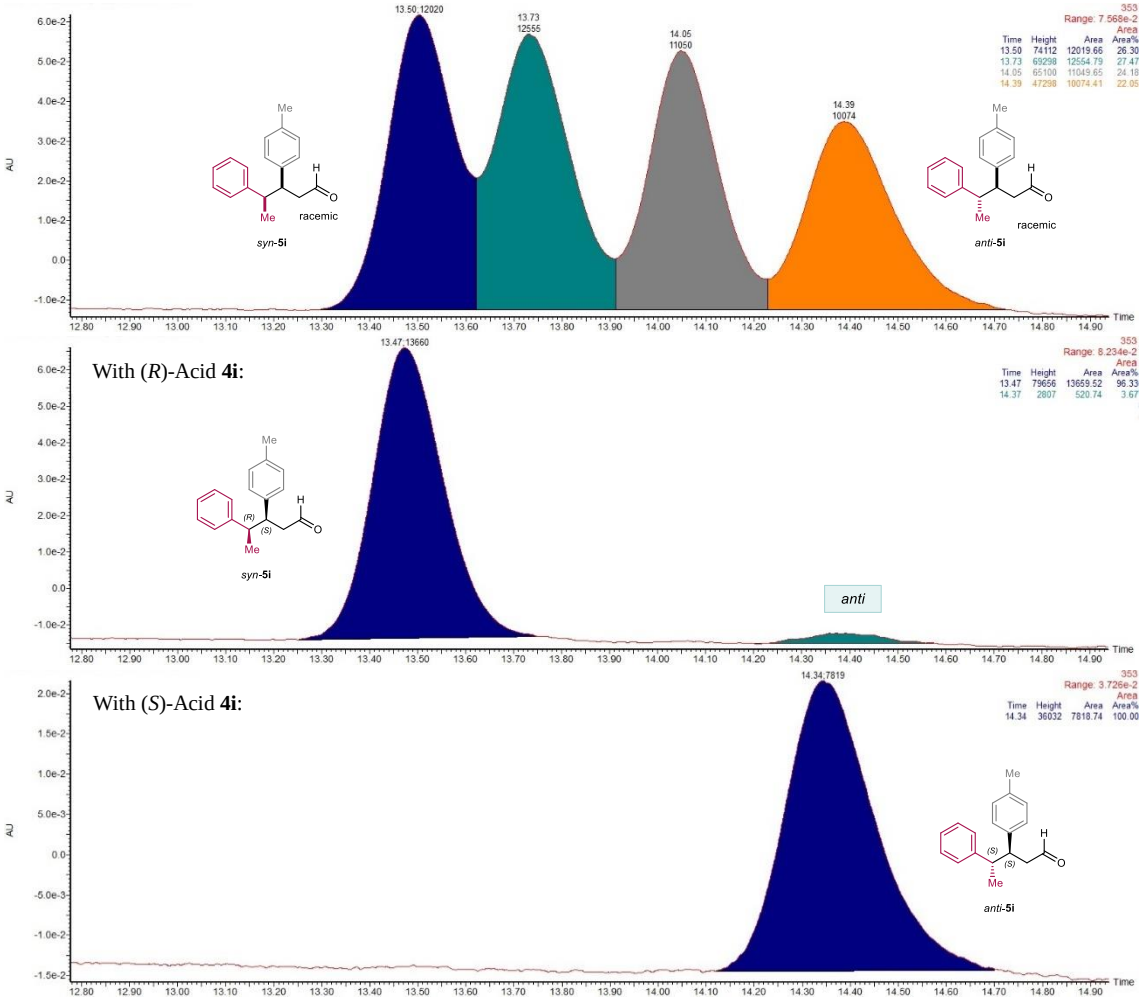
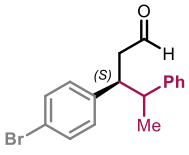


Figure S58. UPC^2 analysis to determine the ee of **5i** formed in the photobiocatalytic process.

(3*S*)-3-(4-Bromophenyl)-4-phenylpentanal (5j)



syn- or *anti*-**5j**

Prepared according to **GP5**, using (*R*)- or (*S*)-2-phenylpropionic acid **4a** (25 µL of a 87.5 mM stock solution in DMSO, 2.2 µmol) and enal **1d** (25 µL of a 25 mM stock solution in DMSO, 0.68 µmol) as substrates in a 10% v/v DMSO/MOPS buffer pH 6.5 mixture. The crude extract was analyzed by GC-FID on HP-5 column. The analytical yield of product **5j** was determined according to the calibration curve given below using mesitylene as the internal standard and as an average of three runs. In case of using (*R*)-**4a** the product *syn*-**5j** (38% yield, 13:87 d.r., >99% ee) was obtained, while the diastereomer *anti*-**5j** (26% yield, 93:7 d.r., >99% ee) was obtained when using (*S*)-**4a**. The enantiomeric excess of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) was determined using UPC^2 analysis on a Daicel Chiralpak IE-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 70:30 CO_2/ EtOH for 5 min; isocratic 70:30 CO_2/EtOH for 10 min, gradient from 70:30 CO_2/EtOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 348 nm: *syn*-**5j**: τ = 10.7 min and *anti*-**5j**: τ = 12.0 min.

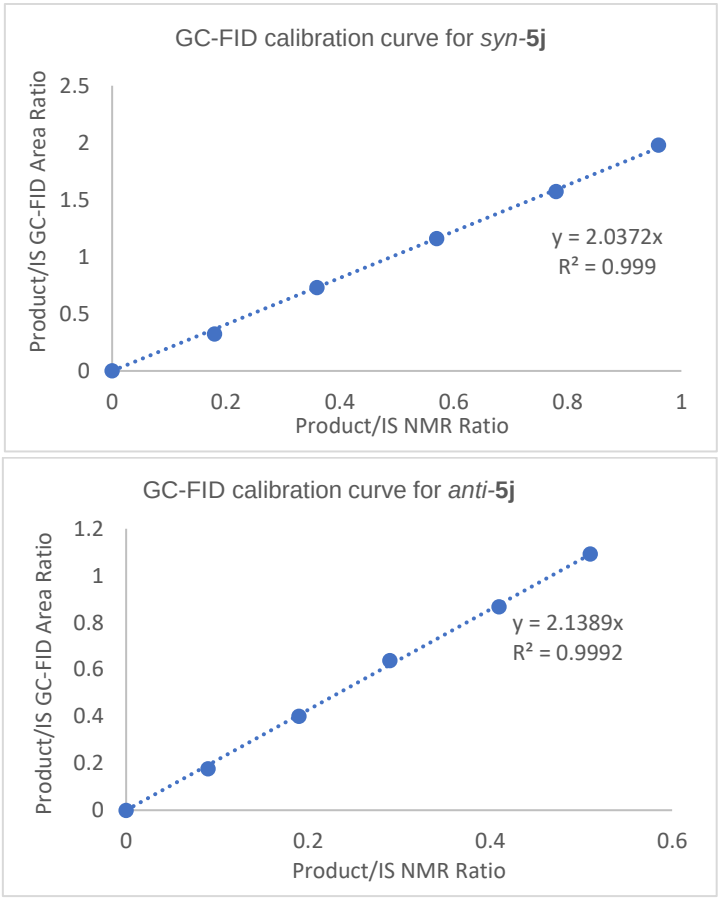
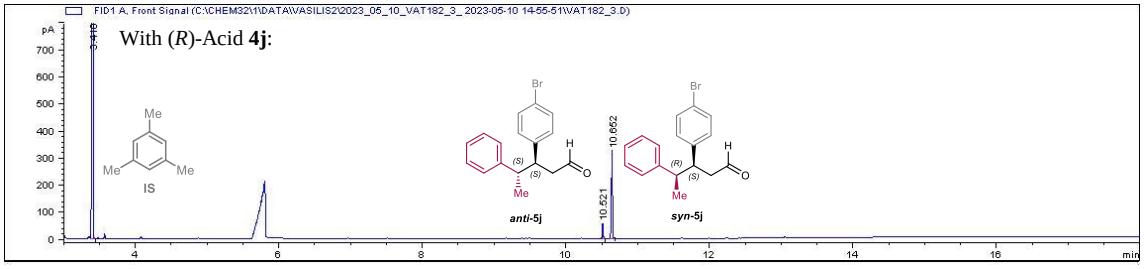


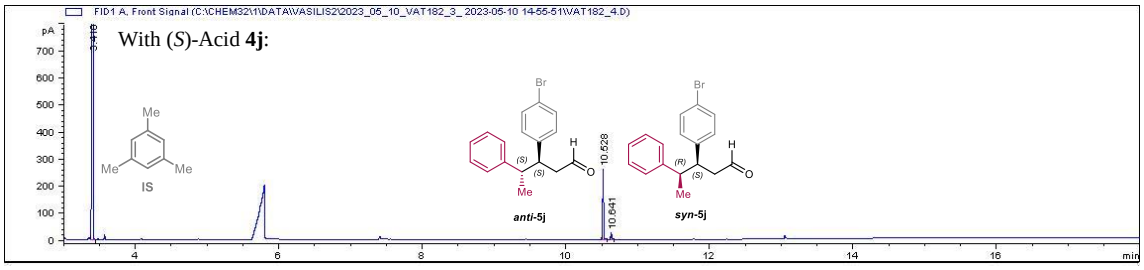
Figure S59. Calibration curves of compounds *syn*-**5j** and *anti*-**5j**. GC-FID calibration curves were obtained from 5mM solutions of the internal standard (IS = 1,3,5-trimethoxybenzene) in ethyl acetate with different concentrations of the corresponding product **5**.



Signal 1: FID1 A, Front Signal

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	3.418	VB	0.0174	2323.17993	2022.57080	85.60126
2	10.521	BB	0.0147	50.02031	54.59217	1.84308
3	10.652	BB	0.0171	340.75510	322.62018	12.55566

Totals : 2713.95534 2399.78315



Signal 1: FID1 A, Front Signal

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	3.418	VB	0.0171	2312.16797	2051.37598	89.35905
2	10.528	BB	0.0147	254.60312	258.25385	9.83972
3	10.641	BB	0.0147	20.73176	22.68293	0.80123

Totals : 2587.50285 2332.31275

Figure S60. GC-FID analysis for determination of the conversion (analytical yield)

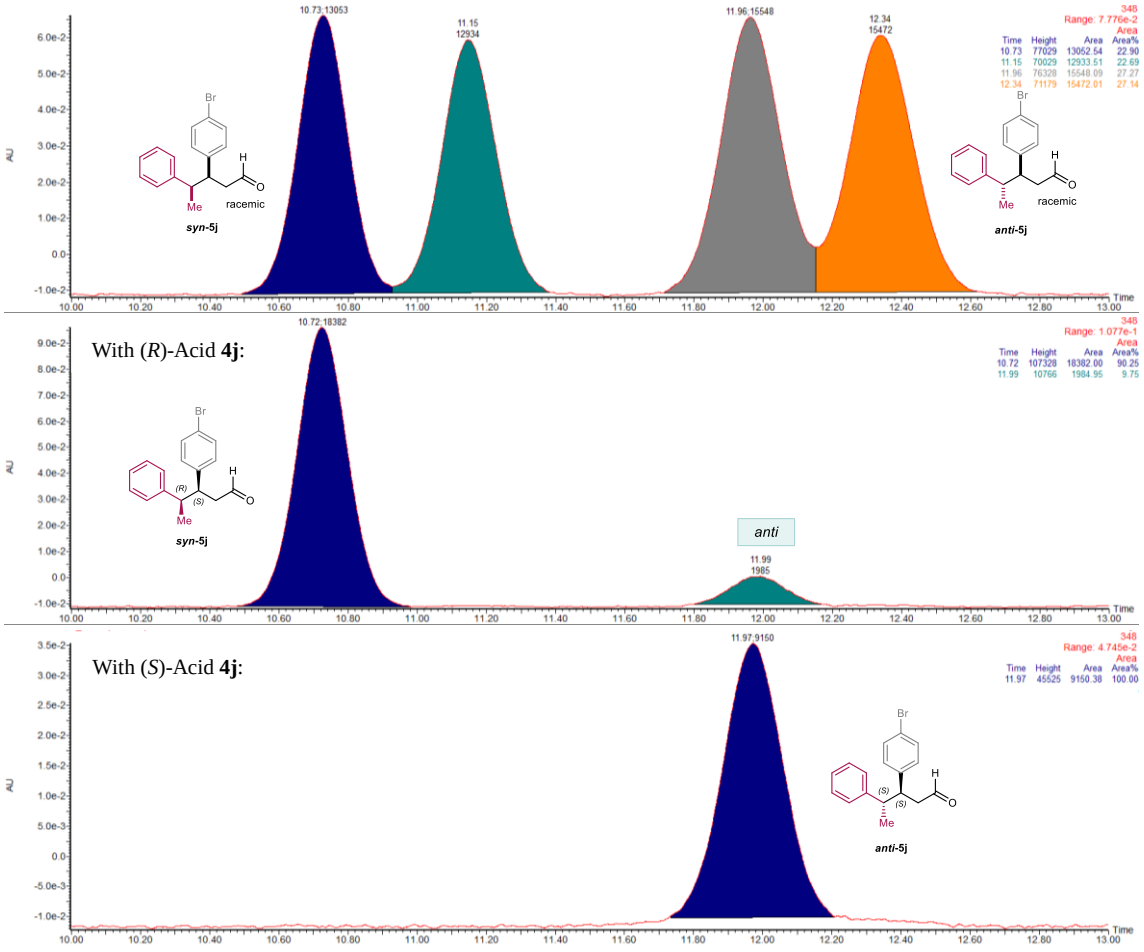
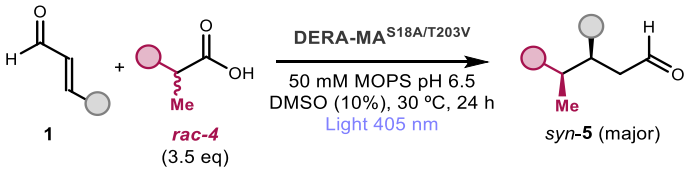


Figure S61. UPC^2 analysis to determine the ee of **5j** formed in the photobiocatalytic process.

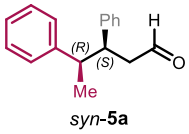
I.4 Analytical Scale Biocatalytic Reactions – Kinetic Resolution Procedure

GP6 – General Procedure for the Analytical Scale of the Kinetic Resolution of Compounds 5



A stock solution of cinnamaldehyde **1** (50 mM) and a stock solution of the corresponding racemic mixture of acid **4** (175 mM) in DMSO were added to a 5 mL glass vial containing 50 mM MOPS buffer pH 6.5. The headspace of the vial was purged with argon and the purified enzyme DERA-MA$^{S18A/T203V}$ (62.5 nmol, 1.0 equiv.) in MOPS buffer pH 6.5 was added to reach the final volume of 500 µL. The vial was then placed in the 3D printed support photoreactor (see Section I.1) and irradiated under stirring for 16 hours. The crude mixture was extracted once with 600 µL ethyl acetate containing 5 mM of the internal standard 1,3,5-trimethoxybenzene or mesitylene. The organic extract was dried over anhydrous $MgSO_4$, filtered and analyzed by GC-FID on HP-5 column. Calibration curves were obtained using the previously synthesized reference compounds **5** and internal standard (1,3,5-trimethoxybenzene or mesitylene). The GC-FID data for the analytical scale reactions were fit in the equation to determine the conversion (analytical yield) and diastereomeric ratio of the products **5**. The enantiomeric excess was determined by UPC^2.

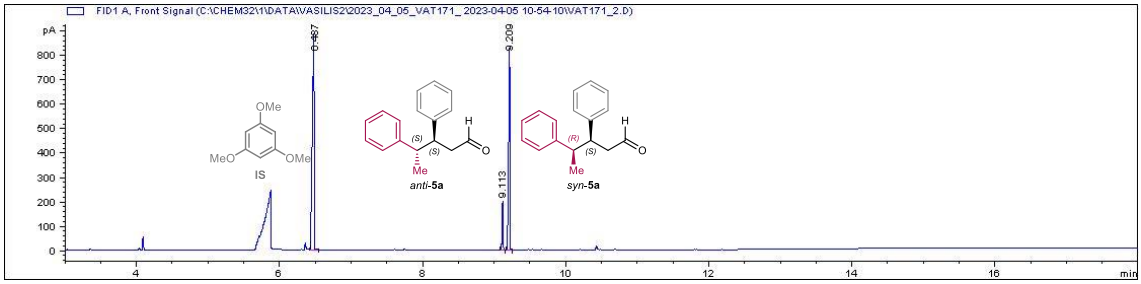
(3*S*,4*R*)-3,4-Diphenylpentanal (5a)



syn-**5a**

Prepared according to **GP6**, using racemic 2-phenylpropionic acid **4a** (25 µL of a 175 mM stock solution in DMSO, 4.4 µmol) and cinnamaldehyde **1a** (25 µL of a 50 mM stock solution in DMSO, 1.25 µmol) as substrates in a 10% v/v DMSO/MOPS buffer pH 6.5 mixture. The crude extract was analyzed by GC-FID on HP-5 column. The analytical yield of product **5a** was determined according to the calibration curve (see I.3) using 1,3,5-trimethoxybenzene as the internal standard and as an average of three runs. The product *syn*-**5a** (67% yield, 5.4:1 d.r., >99% ee) was obtained. The enantiomeric excess of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) was determined using UPC^2 analysis on a Daicel Chiralpak IE-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/*i*-PrOH for 15 min; isocratic 60:40 CO_2/ *i*-PrOH for 8 min, gradient from 60:40 CO_2/*i*-PrOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 345 nm: *syn*-**5a**: τ = 19.2 min and *anti*-**5a**: τ = 21.1 min.

a)



Signal 1: FID1 A, Front Signal

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	6.487	BB	0.0227	1536.07117	881.87726	56.72302
2	9.113	BB	0.0149	185.52129	198.23050	6.85081
3	9.209	BB	0.0168	986.42816	824.22876	36.42617
Totals :				2708.02061	1904.33652	

b)

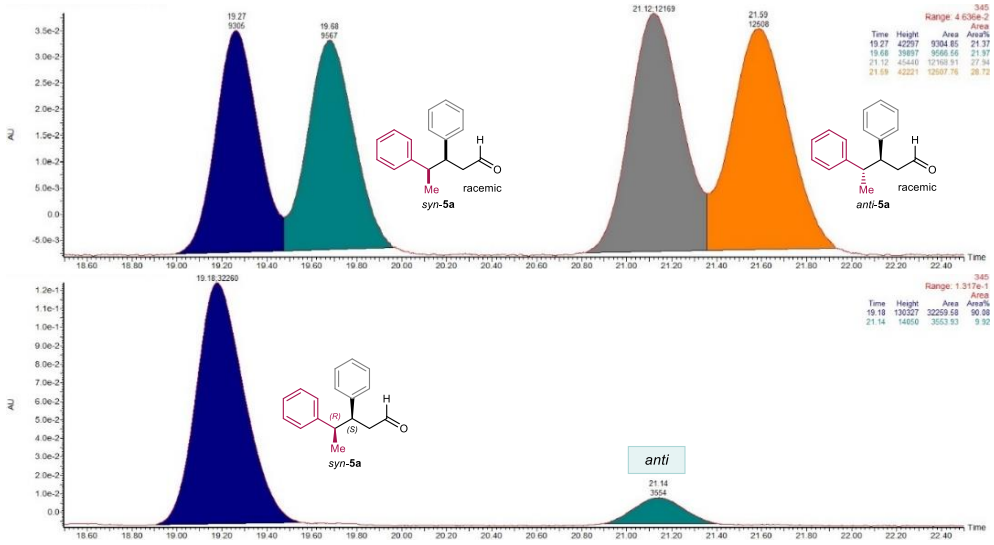
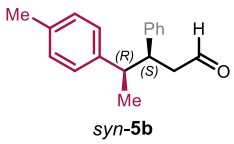


Figure S62. (a) GC-FID analysis of the enzymatic reaction with DERA-MA$^{S18A/T203V}$ for the determination of the conversion (analytical yield) and (b) UPC^2 analysis for determination of the ee.

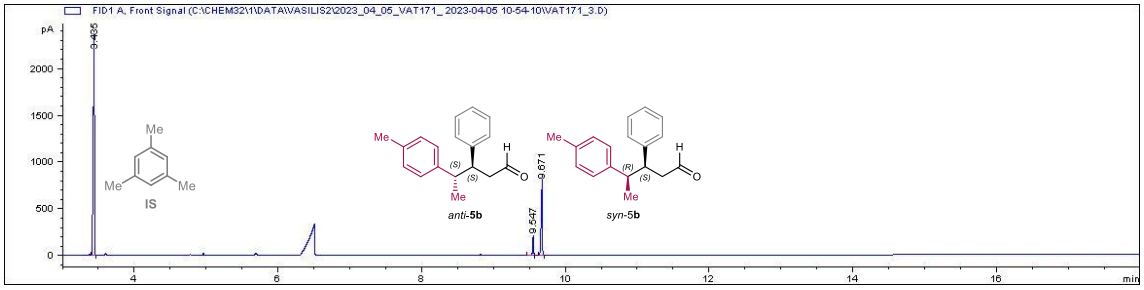
(3*S*,4*R*)-3-Phenyl-4-(p-tolyl)pentanal (5b)



syn-**5b**

Prepared according to **GP6**, using racemic 2-(*p*-tolyl)propanoic acid **4b** (25 µL of a 175 mM stock solution in DMSO, 4.4 µmol) and cinnamaldehyde **1a** (25 µL of a 50 mM stock solution in DMSO, 1.25 µmol) as substrates in a 10% v/v DMSO/MOPS buffer pH 6.5 mixture. The crude extract was analyzed by GC-FID on HP-5 column. The analytical yield of product **5b** was determined according to the calibration curve (see I.3) using mesitylene as the internal standard and as an average of three runs. The product *syn*-**5b** (76% yield, 5.5:1 d.r., >99% ee) was obtained. The enantiomeric excess of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) was determined using UPC^2 analysis on a Daicel Chiralpak IA-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/EtOH for 11 min; isocratic 60:40 CO_2/EtOH for 6 min, gradient from 60:40 CO_2/EtOH to 100% CO_2 for 1 min, flow rate 1.0 mL/min, λ = 352 nm: *syn*-**5b**: τ = 16.5 min.

a)



Signal 1: FID1 A, Front Signal

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	3.435	VB	0.0166	2741.44971	2389.26514	70.29147
2	9.547	BB	0.0150	190.77173	202.54190	4.89144
3	9.671	BB	0.0184	967.89551	785.67462	24.81709
Totals :				3900.11694	3377.48166	

b)

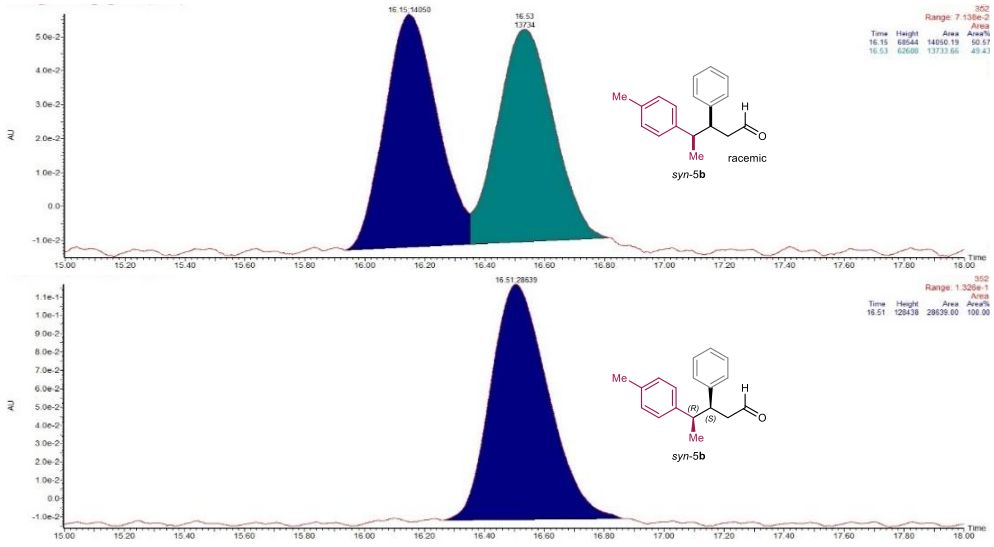
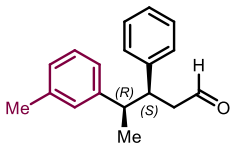


Figure S63. (a) GC-FID analysis of the enzymatic reaction with DERA-MA$^{S18A/T203V}$ for the determination of the conversion (analytical yield) and (b) UPC^2 analysis for determination of the ee.

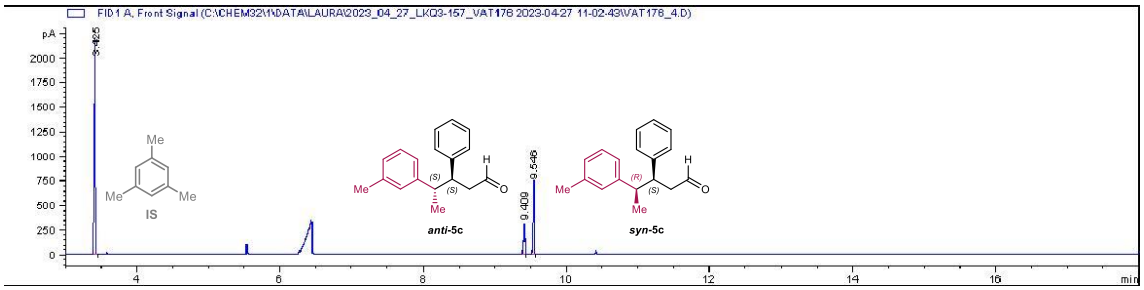
(3*S*,4*R*)-3-Phenyl-4-(*m*-tolyl)pentanal (5c)



syn-**5c**

Prepared according to **GP6**, using racemic 2-(*m*-tolyl)propanoic acid **4c** (25 µL of a 175 mM stock solution in DMSO, 4.4 µmol) and cinnamaldehyde **1a** (25 µL of a 50 mM stock solution in DMSO, 1.25 µmol) as substrates in a 10% v/v DMSO/MOPS buffer pH 6.5 mixture. The crude extract was analyzed by GC-FID on HP-5 column. The analytical yield of product **5c** was determined according to the calibration curve (see I.3) using mesitylene as the internal standard and as an average of three runs. The product *syn*-**5c** (49% yield, 3.1:1 d.r., 95% ee) was obtained. The enantiomeric excess of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) was determined using UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/ EtOH for 13 min; isocratic CO_2/EtOH 60:40 for 2 min, gradient from 60:40 CO_2/EtOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 347 nm: *syn*-**5c**: τ_{major} = 9.89 min and τ_{minor} = 10.30 min; *anti*-**5c**: τ_{major} = 10.7 min and τ_{minor} = 11.2 min.

a)




```
Signal 1: FID1 A, Front Signal

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1   3.425 VB    0.0176 2540.27441 2176.82471 68.60681
   2   9.409 BV    0.0147  286.04416  312.12695  7.72538
   3   9.546 BB    0.0180  876.33783  730.44519 23.66781

Totals :                  3702.65640 3219.39685
```

b)

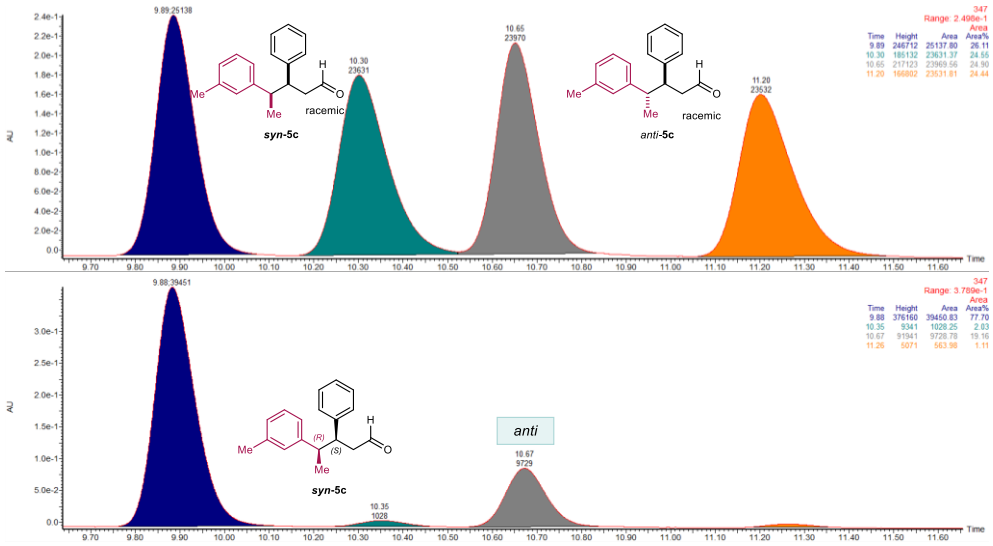
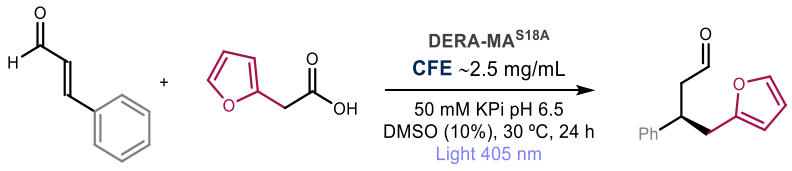


Figure S64. (a) GC-FID analysis of the enzymatic reaction with DERA-MA$^{S18A/T203V}$ for the determination of the conversion (analytical yield) and (b) UPC^2 analysis for determination of the ee.

I.5 Semi-Preparative Scale Biocatalytic Synthesis

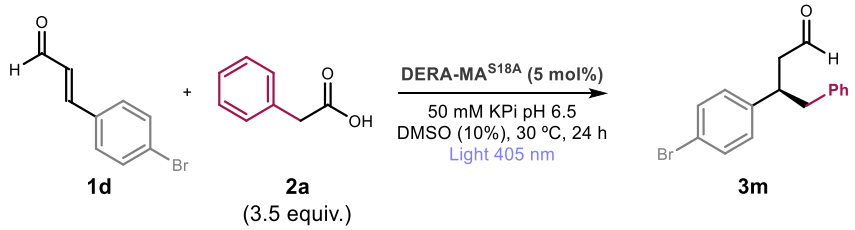
Semi-Preparative Scale Enzymatic Synthesis of (*R*)-3-Phenyl-4-(furan-2-yl)butanal 3j



In the DERA-MA^{S18A}-catalyzed biosynthesis of compounds **3j** on a semi-preparative scale, 2.3 g of *E. Coli* cells containing the overexpressed DERA-MA^{S18A} enzyme were resuspended in 27 mL of 50 mM KPi buffer pH 6.5 and sonicated for 20 min. The lysate was cleared by centrifugation for 20 min at 4ºC and the supernatant collected and used without further purification. In a 50 mL round bottom flask a solution of and cinnamaldehyde **1a** (9.4 µL, 75 µmol, 1.0 equiv.) and furan acetic acid **2j** (33.4 mg, 263 µmol, 3.5 equiv.) in DMSO (3mL) was added to the supernatant to reach the final volume of 30 mL (10% v/v DMSO/water buffer). The reaction mixture was irradiated at 30 ºC in the photoreactor (see section H1.2) for 24 hours. The crude mixture was extracted with ethyl acetate (2 x 15mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (SiO_2, hexante:Et_2O 9:1) to afford product **3j** (8.6 mg, 37.4 µmol, 50% yield, >99% ee,) as a colorless oil. The enantiomers of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) were separated by UPC^2 analysis on a Daicel Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/*i*-PrOH for 5 min; isocratic 60:40 CO_2/*i*-PrOH for 2 min, gradient from 60:40 CO_2/*i*-PrOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 347 nm, **3j**: τ = 6.0 min; $[\alpha]_D^{20}$ = +0.70 (c = 0.275, CH_2Cl_2, >99% ee). The absolute configuration was assigned by comparison with product **3a** (see Section E.3).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.59 (t, *J* = 2.0 Hz, 1H), 7.33 – 7.28 (m, 3H), 7.24 – 7.21 (m, 1H), 7.21 – 7.16 (m, 2H), 6.24 (dd, *J* = 3.2, 1.9 Hz, 1H), 5.92 (dq, *J* = 3.2, 0.8 Hz, 1H), 3.67 – 3.59 (m, 1H), 3.04 – 2.87 (m, 2H), 2.77 (dd, *J* = 7.3, 1.9 Hz, 2H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 201.32, 153.22, 143.20, 141.51, 128.82, 127.43, 127.02, 110.36, 107.19, 49.17, 39.52, 35.39.
HRMS (ESI): Calculated for $[M+Na]^+$ $[C_{14}H_{14}NaO_2]^+$: 237.0886, found: 237.0878.

Semi-Preparative Scale Enzymatic Synthesis of (*R*)-3-(4-Bromophenyl)-4-phenylbutanal (3m)



A stock solution of cinnamaldehyde **1** (0.68 µmol, final concentration of 1.25 mM) and a stock solution of phenylacetic acid **2a** (35.7mg, 263 µmol, 3.5 equiv.) in DMSO (3 mL). were added to a 50 mL round bottom flask containing 50 mM KPi buffer pH 6.5. The purified enzyme DERA-MA$^{S18A/T203A}$ (4.2 mL, 900 nM, 5 mol%) in KPi buffer pH 6.5 was added to reach the final volume of 30 mL. The reaction mixture was irradiated at 30 ºC in the photoreactor (see section H1.2) for 24 hours. The reaction mixture was extracted with ethyl acetate (2 x 15mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (SiO_2, hexante:Et_2O 9:1) to afford product **3m** (4.7 mg, 22.0 µmol, >99% ee, 29% yield) as a colorless oil. The enantiomers of the corresponding 2,4-dinitrophenylhydrazone (obtained upon condensation with 2,4-dinitrophenylhydrazine) were separated by UPC^2 analysis on a Daicel Chiralpak Chiralpak ID-3 column: isocratic 100% CO_2 for 1 min; gradient from 100% CO_2 to 60:40 CO_2/MeOH for 13 min; isocratic 60:40 CO_2/MeOH for 2 min, gradient from 60:40 CO_2/MeOH to 100% CO_2 for 1 min, flow rate 2.0 mL/min, λ = 350 nm, ***3m***: τ = 13.2 min; $[\alpha]_D^{20}$ = +34.9 (c = 0.235, CH_2Cl_2, >99% ee). The absolute configuration was assigned by comparison with product **3a** (see Section E.3).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.60 (t, *J* = 1.7 Hz, 1H), 7.41 – 7.36 (m, 2H), 7.26 – 7.21 (m, 2H), 7.20 – 7.15 (m, 1H), 7.06 – 6.98 (m, 4H), 3.47 (p, *J* = 7.5 Hz, 1H), 2.88 (d, *J* = 7.5 Hz, 2H), 2.75 (dd, *J* = 7.2, 1.8 Hz, 2H).

J. Mechanistic Experiments

J.1 UV/Vis Spectroscopic Studies

The following section reports the UV/Vis spectra of substrates and DERA-MA^{S18A} and DERA-MA^{K167L} used in this study (see Fig 1C of the main paper). The samples for the UV/Vis studies were measured in a 1 cm path length quartz cuvette equipped with a Teflon® septum and analyzed using a Cary60 UV-Vis spectrophotometer. Four samples in 1 mL buffer (50 mM KPi buffer pH 6.5, 10% DMSO), were prepared and measured:

- cinnamaldehyde **1a** (150 µM, 25 µL of a 6.25 mM stock solution, grey line in **Figure S65**)
- DERA-MA^{S18A} (15 µM, green line in **Figure S65**)
- **1a** and DERA-MA^{S18A} (blue line in **Figure S65**)
- **1a**, penylacetic acid **2a** (0.5 mM, 25 µL of a 175 mM stock solution) and DERA-MA^{S18A} (orange line in **Figure S65**)

Neither the enzyme nor cinnamaldehyde **1a** absorb at 405 nm. After formation of the iminium ion within the active site of the enzyme, a bathochromic shift was observed. The absorption spectrum indicates that this species can absorb until approximately 410 nm. Addition of phenylacetic acid **2a** does not lead to a further shift toward higher wavelengths.

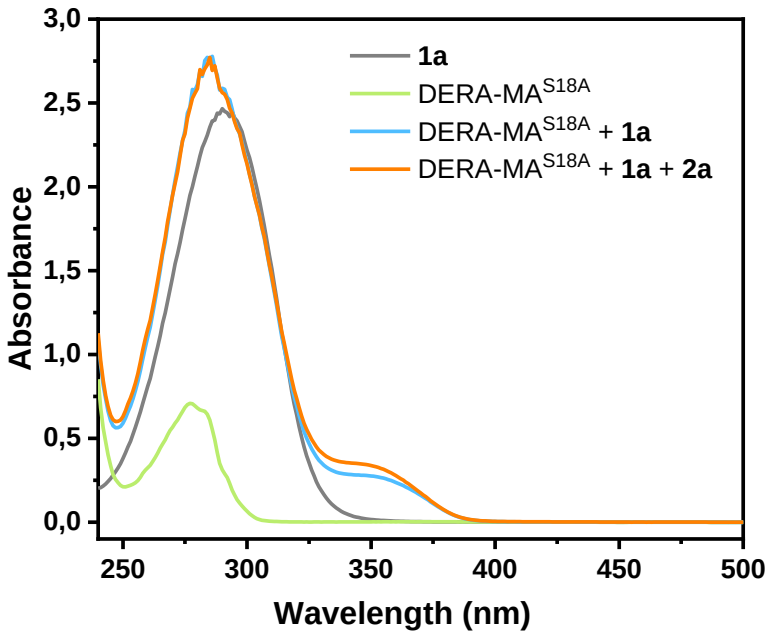


Figure S65. UV-Vis spectra of DERA-MA^{S18A} and reagents **1a** and **2a**, and mixtures thereof.

Additional UV-Vis studies were undertaken to confirm the essential role of K167 in iminium ion formation. Spectra were recorded for the knock-out variant DERA-MA^{K167L}, substrate **1a**, and a mixture of DERA^{K167L} and **1a** (at the same concentration as in the previous studies). In contrast to the results obtained with enzyme DERA-MA^{S18A}, the combination of the variant DERA-MA^{K167L} and cinnamaldehyde **1a** did not induce changes in absorption (**Figure S66**). Therefore, we conclude that in the absence of the lysine residue at position 167 iminium ion formation does not occur.

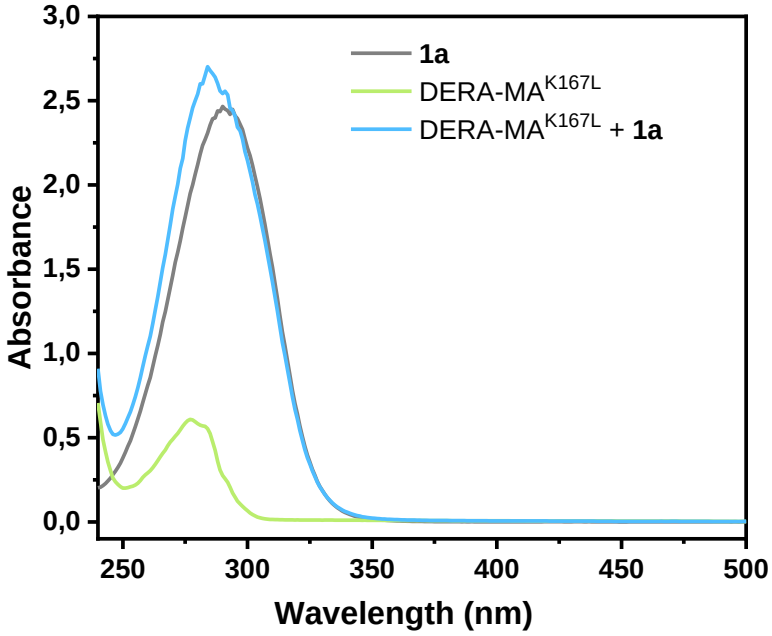


Figure S66. UV-Vis spectra of the knock-out variant DERA-MA^{K167L} and reagent **1a**, and a mixture of the two

J.2 Light On/Off Experiment

A 50 mM stock solution of cinnamaldehyde **1a** (500 µL, 25.0 µmol, 1.0 equiv.) and a 175 mM stock solution of the phenylacetic acid **2a** (500 µL, 87.5 µmol, 3.5 equiv.) in DMSO were added to a 25 mL round bottom flask containing KPi buffer pH 6.5. The headspace of the flask was purged with argon and the purified enzyme DERA-MA^{S18A} (62.5 nmol, 0.05 equiv.) in KPi buffer pH 6.5 was added to reach the final volume of 10 mL. The flask was then placed in the photoreactor (see *Set-up*) and irradiated under stirring for 1h. Two samples of 500 µL were removed from the flask. The remaining reaction mixture was stirred for 30 min in the dark and other two samples were taken from the solution. This light on/off process was repeated for 4 times. The crude mixture was extracted once with 600 µL ethyl acetate containing 5 mM of the internal standard 1,3,5-trimethoxybenzene. The organic extract was dried over anhydrous $MgSO_4$, filtered and analyzed by GC-FID on a HP-5 column. Results are shown in **Table S13** and **Figure S67**.

Table S13. Progress of the DERA-MA^{S18A} –catalyzed reaction of **1a** and **2a** with or without light irradiation.

Entry	Light	Time [h]	Yield [%]
1	**On**	0-1	3.4
2	**Off**	1-1.5	3.2
3	**On**	1.5-2.5	7.1
4	**Off**	2.5-3	7.0
5	**On**	3-4	9.7
6	**Off**	4-4.5	10.0
7	**On**	4.5-5.5	12.8
8	**Off**	5.5-6	12.9

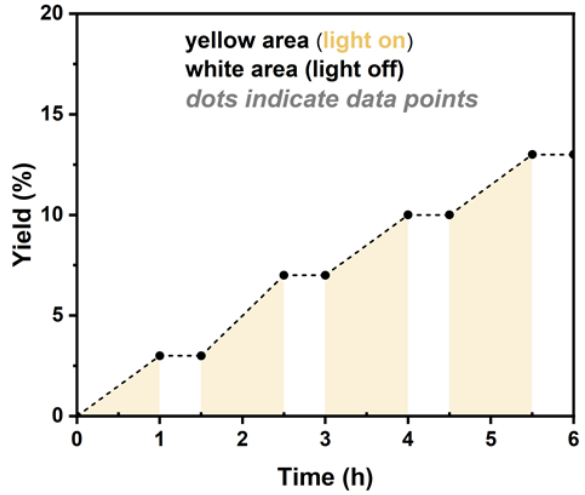


Figure S67. Effect of light irradiation on DERA-MA^{S18A} –catalyzed reaction of **1a** and **2a** during the first 6h. Conversions (analytical yields) determined by GC-FID analysis using the response factor obtained for compound **3a**.

J.3 Enzyme Stability

J.3.1 Mechanical Stress

We conducted studies to explore potential enzyme deactivation pathways. During our investigations, we observed that, over the course of the reaction, the enzyme progressively formed a white precipitate. To elucidate the nature of this process, we examined the enzyme concentration in two differently treated samples without substrates. The first sample, containing only DERA-MA$^{S18A/T203A}$ at a concentration of 3.7 mg/mL, was irradiated with purple light without stirring (depicted by the grey line in **Figure S68**). The results showed minimal impact on enzyme solubility, with the enzyme remaining fully soluble after 24 hours of light irradiation. In contrast, the second sample, subjected to both light irradiation and stirring (360 rpm), exhibited precipitation, with only 21% of the enzyme remaining in the soluble fraction after 24 hours (illustrated by the blue line). These findings suggest that mechanical stress induced by stirring significantly contributes to the enzyme deactivation.

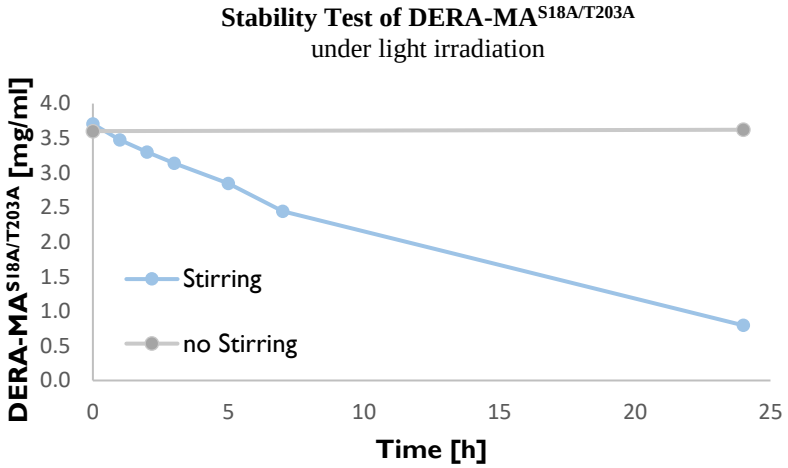
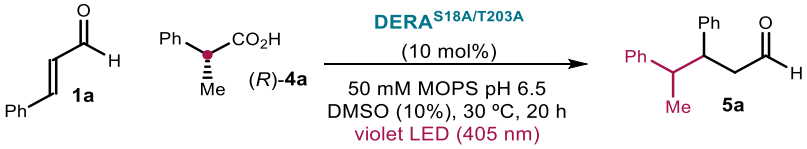


Figure S68. Stability test under violet light irradiation. DERA-MA$^{S18A/T203A}$: 3.7 mg/ml in 50 mM KPi buffer pH 6.5

Additional experiments were conducted to elucidate the role of mechanical stress on enzyme deactivation. Specifically, the behaviour of the enzyme was investigated based on the type of stirring employed, ranging the stirring velocity from 0 (no stirring or shaking) to 750 rpm. The results presented in **Table S14** indicate that the highest yield of product **5a** was achieved at 360 rpm (standard rpm, *the condition used in the best protocol*). In reactions without stirring (0 rpm, entry 1), with low stirring (50 rpm, entry 2), or with higher stirring (750 rpm, entry 4), the yield of product **5a** consistently remained lower compared to that at 360 rpm.

Shaking the reaction vial without a stirring bar resulted in a similar yield compared to the standard 360 rpm (entry 5). Using this setup, the reaction was evaluated employing 5 mol% of enzyme, which provided appreciable but lower reactivity (entry 6). It is noteworthy that in these experiments, complete conversion of cinnamaldehyde **1a** took place, except for the reaction at 750 rpm. This implies that at 750 rpm, the enzyme experienced a loss of activity due to mechanical stress induced by the high stirring speed before consuming all available cinnamaldehyde in the reaction mixture.

Table S14. Effect of stirring on the reaction yield and the conversion of cinnamaldehyde **1a**.



Entry	Stirring (rpm)	yield **5a** (%)	Conversion **1a** (%)
1	0	56	100
2	50	71	100
3	360	77	100
4	750	39	87
5	Shaking (no stirring bar)	74	100
6	Shaking (no stirring bar, ***5% enzyme***)	54	81

In another set of reactions, we investigated if the enzyme was still active at the end of the process, specifically after 20 hours of irradiation. Upon the completion of the model reaction, an additional equivalent of cinnamaldehyde **1a** was introduced, allowing the reaction to proceed for an additional 20 hours (**Figure S69**). Using a stirring bar at 360 rpm, no further product formation was detected. Interestingly, when repeating the same experiment with only shaking the reaction mixture, a 38% increase in **5a** yield was observed. Since shaking is a milder method than stirring, it is hypothesized that less mechanical stress was exerted on the enzyme, reducing the likelihood of its deactivation. This observation suggests that the enzyme could remain active for more extended periods, catalyzing the reaction beyond the initial 20 hours.

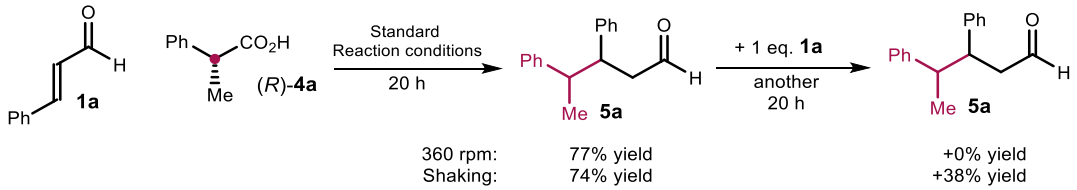


Figure S69. Evaluating enzyme's activity after 20 hours by introducing an additional equivalent of **1a**.

J.3.2 MS Analysis to Identify Deactivation Pathways

The size exclusion chromatography (SEC) coupled with mass spectrometry (SEC-MS) analysis of the protein samples was conducted under native conditions (*59*). Enzymatic samples were buffer-exchanged using Cytiva's Vivaspin 500 columns with a cutoff of 10 kDa MWCO in 400 mM ammonium acetate buffer at pH 5.6. The samples were introduced into a SEC-MS system consisting of a binary solvent manager, a sample manager equipped with a 5 µL sample loop, a column manager, and a PDA detector equipped with an analytical flow cell (V_{det} = 500 nL). For SEC-MS experiments, a similar Waters Acquity system was connected to a Waters Synapt G2 high-resolution mass spectrometer. The SEC–UV-Vis/MS method was performed using one Acquity APC XT 45 A, 4.6 mm ID, 75 mm long, 1.7 µm particles and one Acquity APC XT 125 A, 4.6 mm ID, 75 mm long, 1.7 µm particles; the columns were in series. 10 µL of solute was injected onto the SEC column set operated at a flow of 0.18 mL min^{-1}. Using restriction capillaries, the effluent was split 9:1 to the UV-Vis and MS detector, respectively. The scan time was 1 s positive ESI; time-of-flight MS Resolution mode; capillary voltage, 3.0 kV; sampling cone, 100 V; trap collision energy, 20 eV; source temperature, 100 ˚C; desolvation temperature, 250 ˚C; nitrogen desolvation gas flow, 800 L h^{-1}; nebulizer gas flow, 100 L h^{-1}. Mass calibration was performed using a NaI solution.

The SEC-MS analysis of our protein samples was conducted under native conditions before and after photoirradiation. The double mutant DERA-MA$^{S18A/T203A}$ was measured before irradiation, and the deconvoluted mass was found to be 28,451.7 Da (**Table S15**, entry 1, and **Figure S70a** below), in accordance with the calculated mass of 28,452.46 Da for the enzyme (after cleavage of *N*-terminal methionine). Using the formula below, we calculated the error at 26.7 ppm, which is within the error of the method used (50 ppm), confirming the reliability of the measurements.

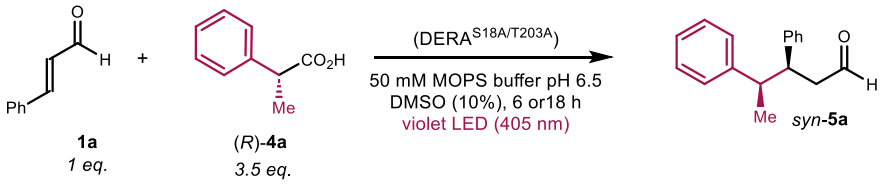
$$(Theoritical\ MW - Measured\ MW \div Theoritical\ MW) \times 10^6$$

We then repeated the same analysis on the protein that was kept under irradiation for 18 hours. This experiment confirmed that light irradiation had no effect on the enzyme's mass (**Table S15**, entry 2, and **Figure S70c**), indicating the *photostability of our enzyme*.

We then performed the model reaction of cinnamaldehyde **1a** and acid (*R*)-**4a** under light irradiation for 6 hours (entry 3) and 18 hours (entry 4 and **Figure S70b**). The soluble protein was analyzed by SEC-MS. Notably, in both samples, the observed mass of the major peak ***increased by 220 Da***.

Control experiments were then performed to understand the origin of this protein change (entries 5-7). All control reactions did not result in a change in the observed protein mass, showing that the modification occurs only under light irradiation and in the presence of both substrates **1a** and (R)-**4a**. For example, when only cinnamaldehyde **1a** was present in the reaction mixture (**Table S15**, entry 5), no change in mass was observed, indicating no enzyme modifications. The same result was obtained for the control reaction in the dark containing both **1a** and **4a** (entry 7 and **Figure S70d**). These latter experiments also indicated that we could not detect the formation of iminium ions bound in the active site by SEC-MS, likely due to the reversible binding of cinnamaldehyde **1a** with lysine K167, and the *lability of the iminium ion under the analysis conditions*.

Table S15. Samples measured by SEC-MS



1a *1 eq.* (*R*)-**4a** *3.5 eq.*

Sample	Enzyme	Light	1a	4a	Time (h)	Dec. Mass	Mass Difference to sample 1
1	+	-	-	-	0	**28451.70**	reference
2	+	+	-	-	18	**28451.97**	0
3	+	+	+	+	6	**28672.18**	220.48
4	+	+	+	+	18	**28672.09**	220.39
5	+	+	+	-	18	**28451.76**	0
6	+	+	-	+	18	**28451.53**	0
7	+	-	+	+	18	**28451.82**	0

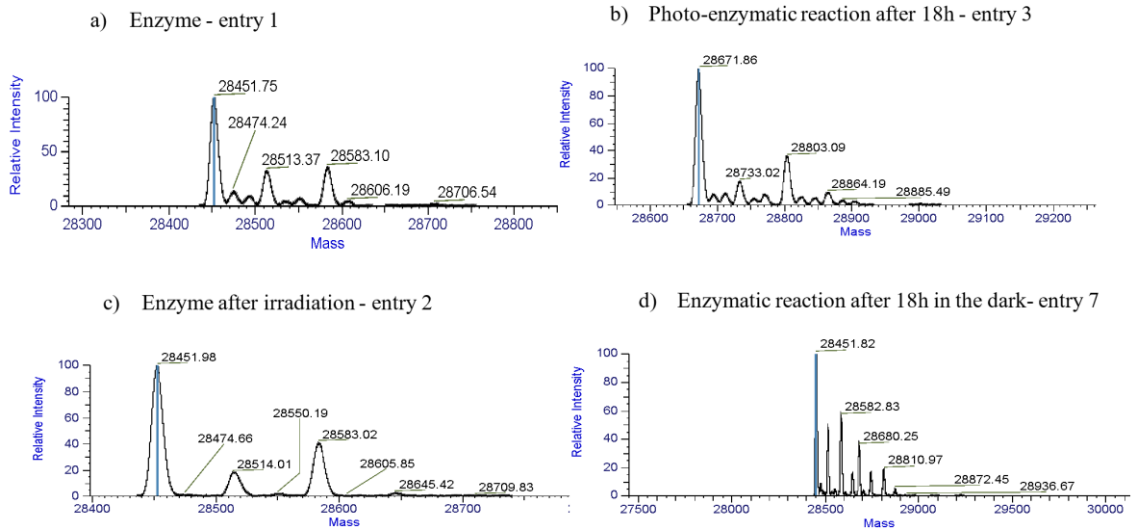


Figure S70. SEC-MS spectra of (**a**) DERA-MA$^{S18A/T203A}$, (**b**) the photoenzymatic reaction with both **1a** and (*R*)-**4a** after 18h, (**c**) DERA-MA$^{S18A/T203A}$ after light irradiation for 18h, and (**d**) the control reaction in the dark containing enzyme, **1a** and (*R*)-**4a** after 18h.

The observed mass increase of 220 (**Figure S70b**, **Table S15**, entries 2 and 3) is consistent with the product formed upon either formal 1,2 or 1,4 addition[1] of the benzylic radical to the iminium ion. However, the latter scenario would lead to the formation of an imine product bound to lysine K167 (**Figure S71**, path A). This path is however unlikely given that SEC-MS analyses in the presence of **1a** (entries 5 and 7) did not show any mass corresponding to the imine, because of the lability and reversible formation of the iminium ion under the analysis conditions.
These studies are therefore consistent with a *radical 1,2-addition to the iminium ion* leading to the *irreversible modification of the catalytic lysine*, forming an amine (**Figure S71**, path B). To further validate this conclusion, we conducted another experiment where, after 18 hours, an aliquot of additional cinnamaldehyde **1a** was added. Due to the enzyme's high affinity toward **1a**, an exchange of a possible imine product with **1a** would be operational. The measured mass of the enzyme remained at 28,672 Da, further confirming an irreversible modification via 1,2 radical addition leading to an amine product.

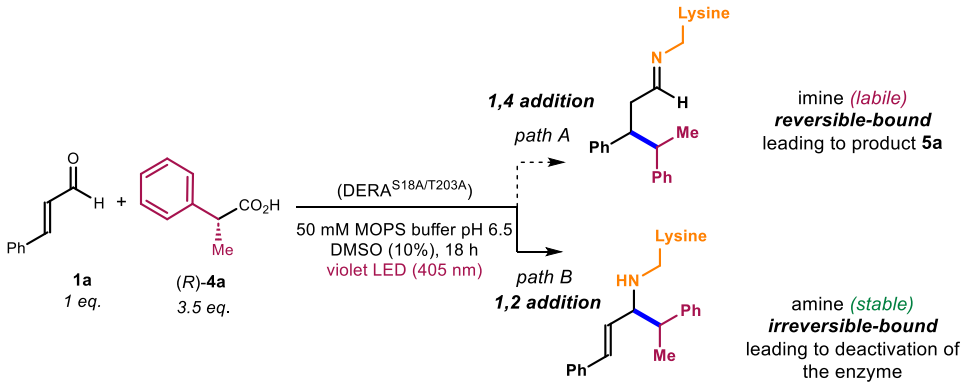


Figure S71. Possible pathways leading to the protein's mass increase detected by SEC-MS analyses.

Collectively, the results discussed in Sections J.3.1 and J.3.2 identified two different reasons for the deactivation of the photoenzymes: *i) mechanical stress* and *ii) irreversible modification* of the lysine residue K167 by radical 1,2-addition to the iminium ion.

[1] *Mechanistic point:* the 1,2 and 1,4 addition terminology is used to describe the type of products formed. It is important to note that the mechanism of bond formation may likely involve radical combination rather than radical addition.

J.4 Byproduct Formation

A careful analysis of the crude reaction mixture was conducted, enabling the identification of two side-products (**Figure S72**). Authentic reference compounds were prepared following a literature procedure (*60*), enabling the unambiguous assignment of the by-products' structures and the estimation of their analytical yields.

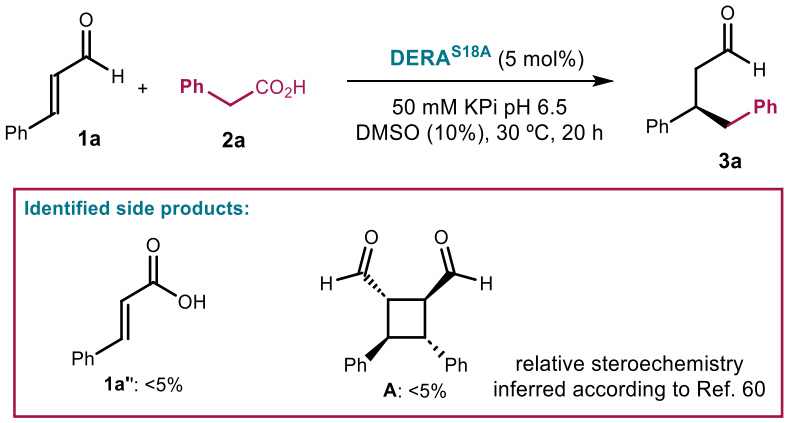


Figure S72. Side products identified in the reaction mixture.

The formation of the acid likely proceeds from the oxidation of cinnamaldehyde **1a**, while the generation of the cycloadduct **A** likely arises through a [2+2] photocycloaddition pathway from the triplet manifold (*61*). Both pathways contribute to lowering the efficiency of the target photobiocatalytic reaction.

K. Circular Dichroism Studies of Engineered Enzyme

Differential absorption of circularly polarized light (circular dichroism) was measured using a Chirascan setup (Applied Photophysics, UK). Purified DERA-MA and DERA$^{S18A/T203A}$ were diluted in 50 mM KH_2PO_4 buffer, pH 6.5 to reach a maximum absorption of ~0.8. CD spectra in the far UV region were recorded from 260 to 190nm at 24ºC using a 2mm quartz cuvette and a bandwidth of 1nm. A solution of 0.6 mg/mL enzyme in buffer was prepared to obtain optimal absorption for the measurement.

CD spectra in the near UV region were recorded from 320 to 260 nm at 24ºC using a 10 mm quartz cuvette and a bandwidth of 1nm. A solution of 1.5 mg/mL enzyme was prepared to obtain optimal absorption for the measurement.

Overall, the CD measurements in the far UV region did not show any changes in the secondary structure of our variant compared to DERA-MA. Additionally, the retention of main minima in the near UV spectra and a similar profile for both enzymes indicate no or insignificant changes in the tertiary structure of our variant (**Figure S73**).

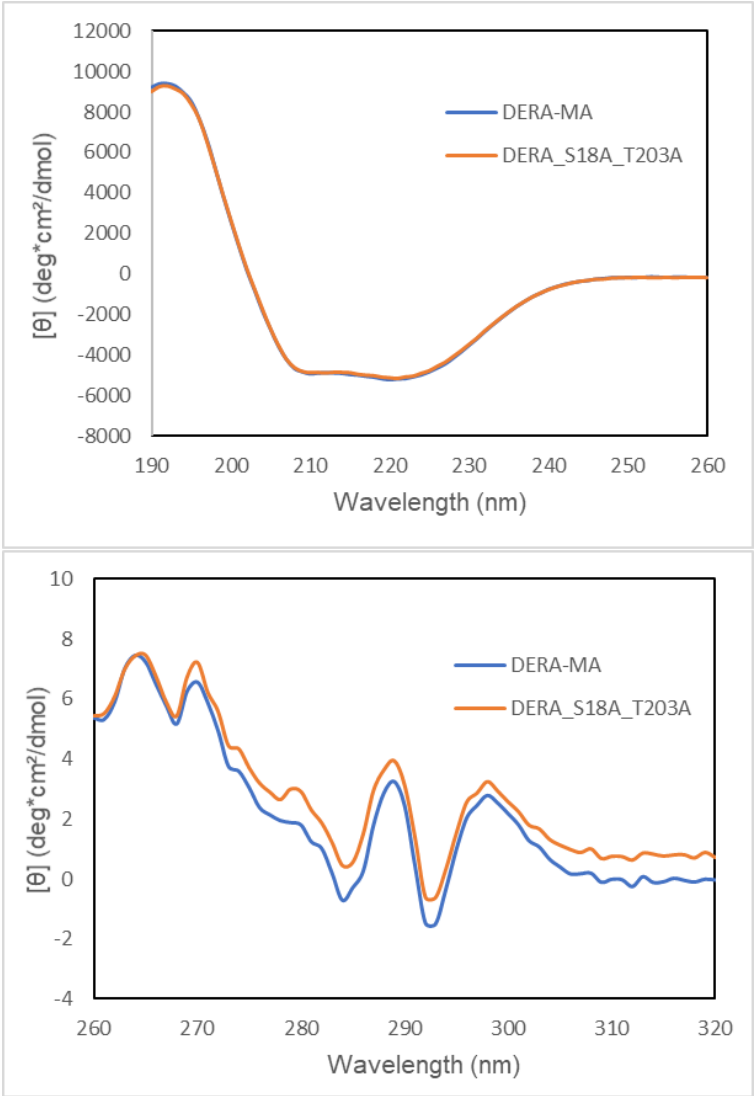
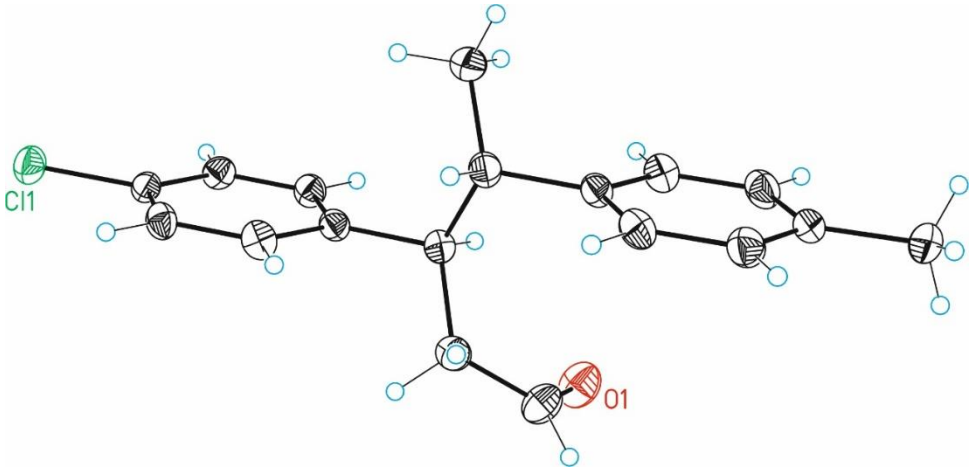


Figure S73. Upper panel, Circular Dichroism (CD) spectra in the far UV region for the comparison of the secondary structures of DERA-MA$^{S18A/T203A}$ and DERA-MA. Lower panel, CD spectra in the near UV region for comparing the tertiary structure of the two enzymes.

L. X-ray crystallographic data

L.1 Crystallographic data for *syn*-5k

Single Crystal X-ray Diffraction Data for Crystals of the compound *syn*-**5k** (prepared using the chiral amine catalyst (*S*)-**A-1**, see section F1) were obtained by slow evaporation of a DCM/hexane solution.



able S14. Crystal data and structure refinement for *syn*-**5k** (*CCDC 2280852*)

Identification code	MBE558F1_a	
Empirical formula	C18 H19 Cl O	
Formula weight	286.78	
Temperature	100(2)K	
Wavelength	0.71073 Å	
Crystal system	orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 5.7579(5)Å	a= 90°.
	b = 7.4820(6)Å	b = 90°.
	c = 35.275(4)Å	g = 90°.
Volume	1519.7(2) $Å^3$	
Z	4	
Density (calculated)	1.253 Mg/m^3	
Absorption coefficient	0.245 mm^{-1}	
F(000)	608	
Crystal size	0.200 x 0.200 x 0.200 mm^3	
Theta range for data collection	3.465 to 29.716°.	
Index ranges	-7<=h<=8,-9<=k<=10,-43<=l<=48	
Reflections collected	22095	
Independent reflections	3989[R(int) = 0.0360]	
Completeness to theta =29.716°	94.9%	
Absorption correction	Multi-scan	
Max. and min. transmission	1.00 and 0.80	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3989/ 0/ 183	
Goodness-of-fit on F^2	1.073	
Final R indices [I>2sigma(I)]	R1 = 0.0356, wR2 = 0.0932	
R indices (all data)	R1 = 0.0379, wR2 = 0.0941	
Flack parameter	x =0.038(15)	
Largest diff. peak and hole	0.446 and -0.166 $e.Å^{-3}$	

Table S16. Bond lengths [Å] and angles [°] for *syn*-**5k**.

Bond lengths Å

Cl1	C1	1.7470(17)
C2	C1	1.380(2)
C2	C3	1.387(2)
C2	H2	0.9500
C1	C6	1.387(3)
O1	C9	1.196(3)
C3	C4	1.393(2)
C3	H3	0.9500
C4	C5	1.398(2)
C4	C7	1.515(2)
C5	C6	1.389(3)
C5	H5	0.9500
C6	H6	0.9500
C7	C8	1.546(2)
C7	C10	1.553(2)
C7	H7	1.0000
C8	C9	1.498(3)
C8	H8A	0.9900
C8	H8B	0.9900
C9	H9	0.9500
C10	C11	1.522(2)
C10	C18	1.531(3)
C10	H10	1.0000
C11	C16	1.390(3)
C11	C12	1.397(2)
C12	C13	1.391(3)
C12	H12	0.9500
C13	C14	1.394(3)
C13	H13	0.9500
C14	C15	1.390(3)
C14	C17	1.516(3)
C15	C16	1.396(3)
C15	H15	0.9500
C16	H16	0.9500
C17	H17A	0.9800
C17	H17B	0.9800
C17	H17C	0.9800
C18	H18A	0.9800
C18	H18B	0.9800
C18	H18C	0.9800

Angles

C1	C2	C3	118.62(17)
C1	C2	H2	120.7
C3	C2	H2	120.7
C2	C1	C6	121.75(16)
C2	C1	Cl1	119.48(14)
C6	C1	Cl1	118.77(14)
C2	C3	C4	121.52(16)
C2	C3	H3	119.2
C4	C3	H3	119.2
C3	C4	C5	118.32(16)
C3	C4	C7	120.67(15)
C5	C4	C7	121.01(15)
C6	C5	C4	121.02(17)
C6	C5	H5	119.5

C4	C5	H5	119.5
C1	C6	C5	118.76(16)
C1	C6	H6	120.6
C5	C6	H6	120.6
C4	C7	C8	111.14(14)
C4	C7	C10	110.94(14)
C8	C7	C10	110.60(14)
C4	C7	H7	108.0
C8	C7	H7	108.0
C10	C7	H7	108.0
C9	C8	C7	115.71(16)
C9	C8	H8A	108.4
C7	C8	H8A	108.4
C9	C8	H8B	108.4
C7	C8	H8B	108.4
H8A	C8	H8B	107.4
O1	C9	C8	126.62(18)
O1	C9	H9	116.7
C8	C9	H9	116.7
C11	C10	C18	110.96(14)
C11	C10	C7	110.93(14)
C18	C10	C7	111.97(15)
C11	C10	H10	107.6
C18	C10	H10	107.6
C7	C10	H10	107.6
C16	C11	C12	117.92(17)
C16	C11	C10	120.73(16)
C12	C11	C10	121.35(16)
C13	C12	C11	120.85(17)
C13	C12	H12	119.6
C11	C12	H12	119.6
C12	C13	C14	121.20(17)
C12	C13	H13	119.4
C14	C13	H13	119.4
C15	C14	C13	117.94(17)
C15	C14	C17	121.63(19)
C13	C14	C17	120.43(19)
C14	C15	C16	120.96(18)
C14	C15	H15	119.5
C16	C15	H15	119.5
C11	C16	C15	121.11(17)
C11	C16	H16	119.4
C15	C16	H16	119.4
C14	C17	H17A	109.5
C14	C17	H17B	109.5
H17A	C17	H17B	109.5
C14	C17	H17C	109.5
H17A	C17	H17C	109.5
H17B	C17	H17C	109.5
C10	C18	H18A	109.5
C10	C18	H18B	109.5
H18A	C18	H18B	109.5
C10	C18	H18C	109.5
H18A	C18	H18C	109.5
H18B	C18	H18C	109.5

Table S17. Torsion angles [°] for *syn*-**5k**.

C3	C2	C1	C6	-0.1(3)
C3	C2	C1	Cl1	-179.83(14)

C1	C2	C3	C4	0.7(3)
C2	C3	C4	C5	-1.3(3)
C2	C3	C4	C7	179.16(16)
C3	C4	C5	C6	1.2(3)
C7	C4	C5	C6	-179.20(16)
C2	C1	C6	C5	0.0(3)
Cl1	C1	C6	C5	179.80(14)
C4	C5	C6	C1	-0.6(3)
C3	C4	C7	C8	-127.56(18)
C5	C4	C7	C8	52.9(2)
C3	C4	C7	C10	108.95(18)
C5	C4	C7	C10	-70.6(2)
C4	C7	C8	C9	142.61(16)
C10	C7	C8	C9	-93.69(19)
C7	C8	C9	O1	-26.6(3)
C4	C7	C10	C11	-178.41(14)
C8	C7	C10	C11	57.78(19)
C4	C7	C10	C18	-53.9(2)
C8	C7	C10	C18	-177.67(16)
C18	C10	C11	C16	126.65(19)
C7	C10	C11	C16	-108.22(19)
C18	C10	C11	C12	-53.3(2)
C7	C10	C11	C12	71.8(2)
C16	C11	C12	C13	-1.6(3)
C10	C11	C12	C13	178.36(18)
C11	C12	C13	C14	0.9(3)
C12	C13	C14	C15	0.2(3)
C12	C13	C14	C17	-179.30(19)
C13	C14	C15	C16	-0.6(3)
C17	C14	C15	C16	178.92(18)
C12	C11	C16	C15	1.3(3)
C10	C11	C16	C15	-178.73(17)
C14	C15	C16	C11	-0.2(3)

L.2 Crystallographic data for *syn*-5e-d1

Single Crystal X-ray Diffraction Data for Crystals of the compound *syn*-**5e-d1** (prepared using DERA-MA^{S18A}, see section I.2) were obtained by slow evaporation of a diethyl ether/hexane solution at 5 ºC.

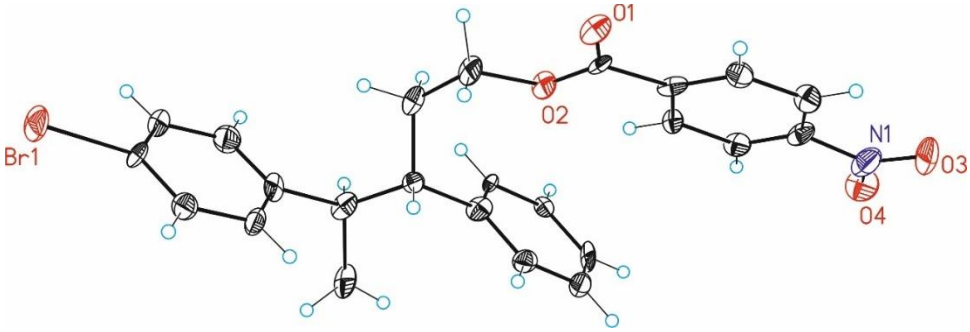


Table S18. Crystal data and structure refinement for *syn*-**5e**-d1 (*CCDC 2281644*)

Identification code	MBELKQ3	
Empirical formula	C24 H22.50 Br N O4	
Formula weight	468.84	
Temperature	100(2)K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	P 21	
Unit cell dimensions	a = 7.5278(3)Å	α= 90°.
	b = 5.7284(2)Å	β = 92.582(4)°.
	c = 24.2837(8)Å	γ = 90°.
Volume	1046.10(7) Å^3	
Z	2	
Density (calculated)	1.488 Mg/m^3	
Absorption coefficient	1.996 mm^{-1}	
F(000)	481	
Crystal size	0.200 x 0.050 x 0.010 mm^3	
Theta range for data collection	2.519 to 29.179°.	
Index ranges	-9<=h<=10,-7<=k<=7,-32<=l<=32	
Reflections collected	15056	
Independent reflections	4872[R(int) = 0.0493]	
Completeness to theta =29.179°	91.5%	
Absorption correction	Multi-scan	
Max. and min. transmission	1.00 and 0.84	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4872/ 61/ 521	
Goodness-of-fit on F^2	1.039	
Final R indices [I>2sigma(I)]	R1 = 0.0362, wR2 = 0.0885	
R indices (all data)	R1 = 0.0455, wR2 = 0.0934	
Flack parameter	x =-0.009(9)	
Largest diff. peak and hole	0.708 and -0.499 e.Å^{-3}	

Table S19. Bond lengths [Å] and angles [°] for *syn*-**5e**-d1.

Bond lengths		
Br1	C1'	1.896(18)
Br1	C1	1.918(18)

O1	C24	1.227(19)
O2	C24	1.30(2)
O2	C17	1.454(11)
O3	N1	1.243(19)
O4	N1	1.18(2)
N1	C21	1.455(19)
C1	C2	1.37(2)
C1	C6	1.380(19)
C2	C3	1.394(15)
C2	H2	0.9500
C3	C4	1.370(17)
C3	H3	0.9500
C4	C5	1.40(2)
C4	C7	1.530(10)
C5	C6	1.391(14)
C5	H5	0.9500
C6	H6	0.9500
C7	C8	1.43(3)
C7	C9	1.555(15)
C7	H7	1.0000
C8	H8A	0.9500
C8	H8B	0.9500
C9	C16	1.522(13)
C9	C10	1.537(11)
C9	H9	1.0000
C10	C11	1.3900
C10	C15	1.3900
C11	C12	1.3900
C11	H11	0.9500
C12	C13	1.3900
C12	H12	0.9500
C13	C14	1.3900
C13	H13	0.9500
C14	C15	1.3900
C14	H14	0.9500
C15	H15	0.9500
C16	C17	1.520(12)
C16	H16A	0.9900
C16	H16B	0.9900
C17	H17A	0.9900
C17	H17B	0.9900
C18	C23	1.365(15)
C18	C19	1.39(2)
C18	C24	1.48(2)
C19	C20	1.40(3)
C19	H19	0.9500
C20	C21	1.355(18)
C20	H20	0.9500
C21	C22	1.418(17)
C22	C23	1.385(16)
C22	H22	0.9500
C23	H23	0.9500
O1'	C18'	1.353(18)
O1'	C17'	1.445(14)
O2'	C18'	1.188(13)
O3'	N1'	1.252(14)
O4'	N1'	1.198(19)
N1'	C22'	1.501(15)
C1'	C2'	1.36(2)
C1'	C6'	1.406(19)

C2'	C3'	1.384(12)
C2'	H2'	0.9500
C3'	C4'	1.413(15)
C3'	H3'	0.9500
C4'	C5'	1.382(12)
C4'	C7'	1.526(11)
C5'	C6'	1.386(15)
C5'	H5'	0.9500
C6'	H6'	0.9500
C7'	C8'	1.51(3)
C7'	C9'	1.551(13)
C7'	H7'	1.0000
C8'	H8'A	0.9800
C8'	H8'B	0.9800
C8'	H8'C	0.9800
C9'	C10'	1.501(12)
C9'	C16'	1.530(12)
C9'	H9'	1.0000
C10'	C15'	1.396(15)
C10'	C11'	1.413(11)
C11'	C12'	1.386(12)
C11'	H11'	0.9500
C12'	C13'	1.374(13)
C12'	H12'	0.9500
C13'	C14'	1.37(2)
C13'	H13'	0.9500
C14'	C15'	1.373(14)
C14'	H14A	0.9900
C14'	H14B	0.9900
C15'	H15A	0.9900
C15'	H15B	0.9900
C16'	C17'	1.526(12)
C16'	H16C	0.9900
C16'	H16D	0.9900
C17'	H17C	0.9900
C17'	H17D	0.9900
C18'	C19'	1.509(16)
C19'	C24'	1.38(3)
C19'	C20'	1.393(14)
C20'	C21'	1.396(16)
C20'	H20'	0.9500
C21'	C22'	1.341(19)
C21'	H21'	0.9500
C22'	C23'	1.402(18)
C23'	C24'	1.37(3)
C23'	H23'	0.9500
C24'	H24'	0.9500

Angles

C24	O2	C17	114.9(10)
O4	N1	O3	121.9(19)
O4	N1	C21	119.7(14)
O3	N1	C21	118.3(19)
C2	C1	C6	121.4(14)
C2	C1	Br1	116.4(11)
C6	C1	Br1	122.2(12)
C1	C2	C3	119.5(11)
C1	C2	H2	120.2
C3	C2	H2	120.2
C4	C3	C2	120.5(10)

C4 C3 H3 119.8
C2 C3 H3 119.8
C3 C4 C5 119.5(8)
C3 C4 C7 120.7(13)
C5 C4 C7 119.8(11)
C6 C5 C4 120.2(9)
C6 C5 H5 119.9
C4 C5 H5 119.9
C1 C6 C5 118.9(11)
C1 C6 H6 120.5
C5 C6 H6 120.5
C8 C7 C4 106.4(13)
C8 C7 C9 108.4(14)
C4 C7 C9 112.8(10)
C8 C7 H7 109.7
C4 C7 H7 109.7
C9 C7 H7 109.7
C7 C8 H8A 120.0
C7 C8 H8B 120.0
H8A C8 H8B 120.0
C16 C9 C10 113.8(7)
C16 C9 C7 111.0(7)
C10 C9 C7 110.8(7)
C16 C9 H9 106.9
C10 C9 H9 106.9
C7 C9 H9 106.9
C11 C10 C15 120.0
C11 C10 C9 119.1(6)
C15 C10 C9 120.8(6)
C12 C11 C10 120.0
C12 C11 H11 120.0
C10 C11 H11 120.0
C11 C12 C13 120.0
C11 C12 H12 120.0
C13 C12 H12 120.0
C14 C13 C12 120.0
C14 C13 H13 120.0
C12 C13 H13 120.0
C13 C14 C15 120.0
C13 C14 H14 120.0
C15 C14 H14 120.0
C14 C15 C10 120.0
C14 C15 H15 120.0
C10 C15 H15 120.0
C17 C16 C9 115.8(7)
C17 C16 H16A 108.3
C9 C16 H16A 108.3
C17 C16 H16B 108.3
C9 C16 H16B 108.3
H16A C16 H16B 107.4
O2 C17 C16 110.3(7)
O2 C17 H17A 109.6
C16 C17 H17A 109.6
O2 C17 H17B 109.6
C16 C17 H17B 109.6
H17A C17 H17B 108.1
C23 C18 C19 119.5(15)
C23 C18 C24 120.1(11)
C19 C18 C24 120.2(15)
C18 C19 C20 119.9(19)

C18 C19 H19 120.0
C20 C19 H19 120.0
C21 C20 C19 118.9(14)
C21 C20 H20 120.6
C19 C20 H20 120.6
C20 C21 C22 122.9(11)
C20 C21 N1 119.1(12)
C22 C21 N1 117.9(13)
C23 C22 C21 115.8(11)
C23 C22 H22 122.1
C21 C22 H22 122.1
C18 C23 C22 123.0(11)
C18 C23 H23 118.5
C22 C23 H23 118.5
O1 C24 O2 124.8(15)
O1 C24 C18 121.9(14)
O2 C24 C18 113.3(13)
C18' O1' C17' 116.5(10)
O4' N1' O3' 126.5(13)
O4' N1' C22' 116.3(11)
O3' N1' C22' 117.2(11)
C2' C1' C6' 122.2(14)
C2' C1' Br1 120.0(12)
C6' C1' Br1 117.7(11)
C1' C2' C3' 118.8(11)
C1' C2' H2' 120.6
C3' C2' H2' 120.6
C2' C3' C4' 120.9(8)
C2' C3' H3' 119.5
C4' C3' H3' 119.5
C5' C4' C3' 118.9(8)
C5' C4' C7' 121.3(10)
C3' C4' C7' 119.7(8)
C4' C5' C6' 120.6(9)
C4' C5' H5' 119.7
C6' C5' H5' 119.7
C5' C6' C1' 118.6(11)
C5' C6' H6' 120.7
C1' C6' H6' 120.7
C8' C7' C4' 116.5(12)
C8' C7' C9' 111.9(12)
C4' C7' C9' 111.8(7)
C8' C7' H7' 105.2
C4' C7' H7' 105.2
C9' C7' H7' 105.2
C7' C8' H8'A 109.5
C7' C8' H8'B 109.5
H8'A C8' H8'B 109.5
C7' C8' H8'C 109.5
H8'A C8' H8'C 109.5
H8'B C8' H8'C 109.5
C10' C9' C16' 112.6(7)
C10' C9' C7' 110.4(8)
C16' C9' C7' 111.7(7)
C10' C9' H9' 107.3
C16' C9' H9' 107.3
C7' C9' H9' 107.3
C15' C10' C11' 115.4(8)
C15' C10' C9' 121.5(9)
C11' C10' C9' 123.0(7)

C12'	C11'	C10'	121.3(7)
C12'	C11'	H11'	119.4
C10'	C11'	H11'	119.4
C13'	C12'	C11'	120.6(8)
C13'	C12'	H12'	119.7
C11'	C12'	H12'	119.7
C14'	C13'	C12'	119.7(8)
C14'	C13'	H13'	120.1
C12'	C13'	H13'	120.1
C13'	C14'	C15'	119.7(12)
C13'	C14'	H14A	107.4
C15'	C14'	H14A	107.4
C13'	C14'	H14B	107.4
C15'	C14'	H14B	107.4
H14A	C14'	H14B	106.9
C14'	C15'	C10'	123.3(12)
C14'	C15'	H15A	106.5
C10'	C15'	H15A	106.5
C14'	C15'	H15B	106.5
C10'	C15'	H15B	106.5
H15A	C15'	H15B	106.5
C17'	C16'	C9'	115.2(7)
C17'	C16'	H16C	108.5
C9'	C16'	H16C	108.5
C17'	C16'	H16D	108.5
C9'	C16'	H16D	108.5
H16C	C16'	H16D	107.5
O1'	C17'	C16'	110.9(7)
O1'	C17'	H17C	109.5
C16'	C17'	H17C	109.5
O1'	C17'	H17D	109.5
C16'	C17'	H17D	109.5
H17C	C17'	H17D	108.0
O2'	C18'	O1'	123.9(13)
O2'	C18'	C19'	124.4(11)
O1'	C18'	C19'	111.6(9)
C24'	C19'	C20'	121.5(14)
C24'	C19'	C18'	121.7(14)
C20'	C19'	C18'	116.6(10)
C19'	C20'	C21'	117.5(11)
C19'	C20'	H20'	121.3
C21'	C20'	H20'	121.3
C22'	C21'	C20'	119.8(12)
C22'	C21'	H21'	120.1
C20'	C21'	H21'	120.1
C21'	C22'	C23'	123.5(11)
C21'	C22'	N1'	118.9(11)
C23'	C22'	N1'	117.6(11)
C24'	C23'	C22'	116.7(15)
C24'	C23'	H23'	121.7
C22'	C23'	H23'	121.7
C23'	C24'	C19'	121(2)
C23'	C24'	H24'	119.5
C19'	C24'	H24'	119.5

Table S20. Torsion angles [°] for *syn*-**5e**-d1.

C6	C1	C2	C3	-2(2)
Br1	C1	C2	C3	176.6(9)
C1	C2	C3	C4	2.2(18)

C2	C3	C4	C5	-1.8(16)
C2	C3	C4	C7	177.4(9)
C3	C4	C5	C6	1.3(16)
C7	C4	C5	C6	-177.9(9)
C2	C1	C6	C5	2(2)
Br1	C1	C6	C5	-177.0(9)
C4	C5	C6	C1	-1.2(16)
C3	C4	C7	C8	-125.4(15)
C5	C4	C7	C8	53.7(17)
C3	C4	C7	C9	115.7(12)
C5	C4	C7	C9	-65.1(10)
C8	C7	C9	C16	-175.8(13)
C4	C7	C9	C16	-58.1(11)
C8	C7	C9	C10	56.7(14)
C4	C7	C9	C10	174.3(8)
C16	C9	C10	C11	-61.1(9)
C7	C9	C10	C11	64.9(8)
C16	C9	C10	C15	121.2(7)
C7	C9	C10	C15	-112.8(7)
C15	C10	C11	C12	0.0
C9	C10	C11	C12	-177.7(8)
C10	C11	C12	C13	0.0
C11	C12	C13	C14	0.0
C12	C13	C14	C15	0.0
C13	C14	C15	C10	0.0
C11	C10	C15	C14	0.0
C9	C10	C15	C14	177.6(8)
C10	C9	C16	C17	-69.8(9)
C7	C9	C16	C17	164.3(7)
C24	O2	C17	C16	-176.3(10)
C9	C16	C17	O2	64.3(10)
C23	C18	C19	C20	0(3)
C24	C18	C19	C20	-175.3(15)
C18	C19	C20	C21	0(3)
C19	C20	C21	C22	1(2)
C19	C20	C21	N1	176.2(16)
O4	N1	C21	C20	8(2)
O3	N1	C21	C20	-175.7(16)
O4	N1	C21	C22	-175.7(14)
O3	N1	C21	C22	0(2)
C20	C21	C22	C23	-0.7(18)
N1	C21	C22	C23	-176.5(12)
C19	C18	C23	C22	0(2)
C24	C18	C23	C22	175.1(11)
C21	C22	C23	C18	0.7(18)
C17	O2	C24	O1	-4(2)
C17	O2	C24	C18	175.1(8)
C23	C18	C24	O1	5.3(18)
C19	C18	C24	O1	-179.2(15)
C23	C18	C24	O2	-174.1(11)
C19	C18	C24	O2	1(2)
C6'	C1'	C2'	C3'	1.2(19)
Br1	C1'	C2'	C3'	-174.2(8)
C1'	C2'	C3'	C4'	-0.1(15)
C2'	C3'	C4'	C5'	-0.6(13)
C2'	C3'	C4'	C7'	175.9(8)
C3'	C4'	C5'	C6'	0.2(14)
C7'	C4'	C5'	C6'	-176.2(8)
C4'	C5'	C6'	C1'	0.8(16)
C2'	C1'	C6'	C5'	-2(2)

Br1	C1'	C6'	C5'	173.9(9)
C5'	C4'	C7'	C8'	70.2(15)
C3'	C4'	C7'	C8'	-106.2(14)
C5'	C4'	C7'	C9'	-60.2(10)
C3'	C4'	C7'	C9'	123.3(8)
C8'	C7'	C9'	C10'	46.1(13)
C4'	C7'	C9'	C10'	178.9(7)
C8'	C7'	C9'	C16'	172.2(12)
C4'	C7'	C9'	C16'	-55.0(10)
C16'	C9'	C10'	C15'	117.8(10)
C7'	C9'	C10'	C15'	-116.7(10)
C16'	C9'	C10'	C11'	-65.4(12)
C7'	C9'	C10'	C11'	60.1(11)
C15'	C10'	C11'	C12'	-2.1(12)
C9'	C10'	C11'	C12'	-179.1(9)
C10'	C11'	C12'	C13'	0.9(13)
C11'	C12'	C13'	C14'	2.0(15)
C12'	C13'	C14'	C15'	-3.6(17)
C13'	C14'	C15'	C10'	2.4(17)
C11'	C10'	C15'	C14'	0.5(15)
C9'	C10'	C15'	C14'	177.5(11)
C10'	C9'	C16'	C17'	-67.2(10)
C7'	C9'	C16'	C17'	168.0(7)
C18'	O1'	C17'	C16'	92.9(11)
C9'	C16'	C17'	O1'	74.4(10)
C17'	O1'	C18'	O2'	-0.7(19)
C17'	O1'	C18'	C19'	-176.8(9)
O2'	C18'	C19'	C24'	-162.3(17)
O1'	C18'	C19'	C24'	13.8(19)
O2'	C18'	C19'	C20'	13.4(18)
O1'	C18'	C19'	C20'	-170.5(11)
C24'	C19'	C20'	C21'	-1(2)
C18'	C19'	C20'	C21'	-177.2(10)
C19'	C20'	C21'	C22'	2.3(17)
C20'	C21'	C22'	C23'	-3.2(19)
C20'	C21'	C22'	N1'	178.1(11)
O4'	N1'	C22'	C21'	-7.8(19)
O3'	N1'	C22'	C21'	174.9(12)
O4'	N1'	C22'	C23'	173.5(14)
O3'	N1'	C22'	C23'	-3.9(17)
C21'	C22'	C23'	C24'	3(2)
N1'	C22'	C23'	C24'	-178.2(15)
C22'	C23'	C24'	C19'	-2(3)
C20'	C19'	C24'	C23'	1(3)
C18'	C19'	C24'	C23'	177.0(16)

Symmetry operations

1	'x, y, z'
2	'-x, y+1/2, -z'

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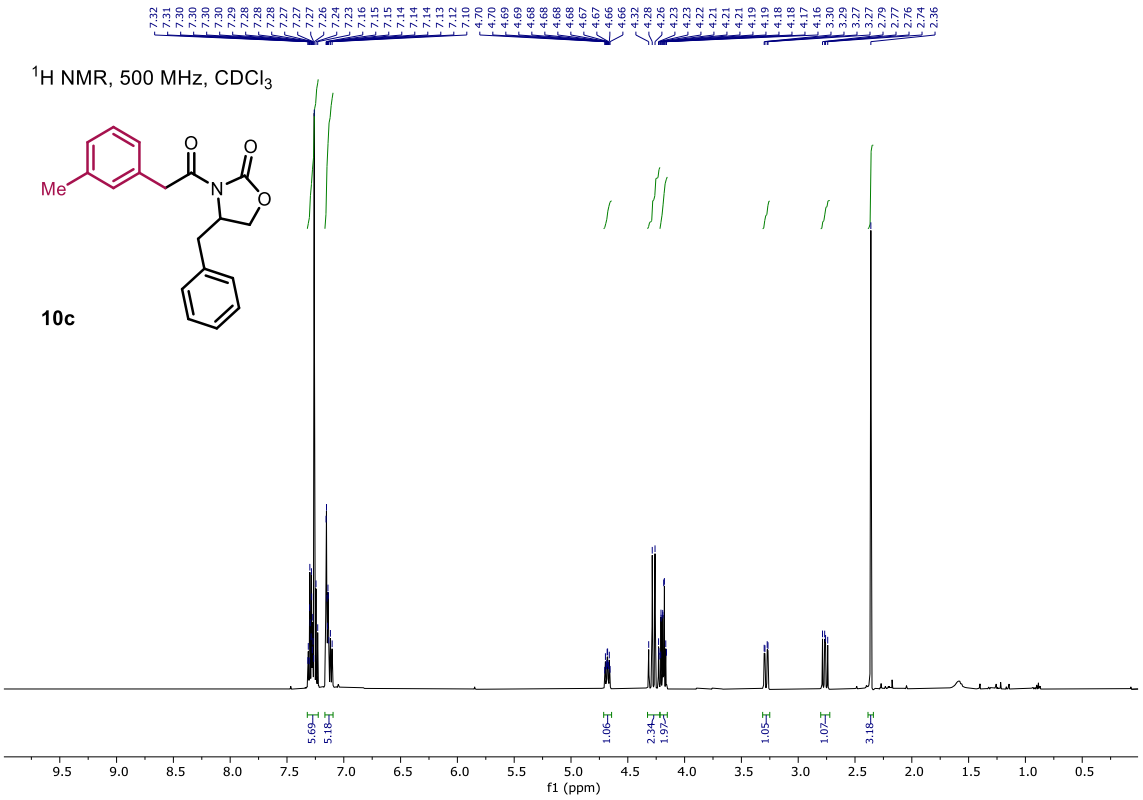
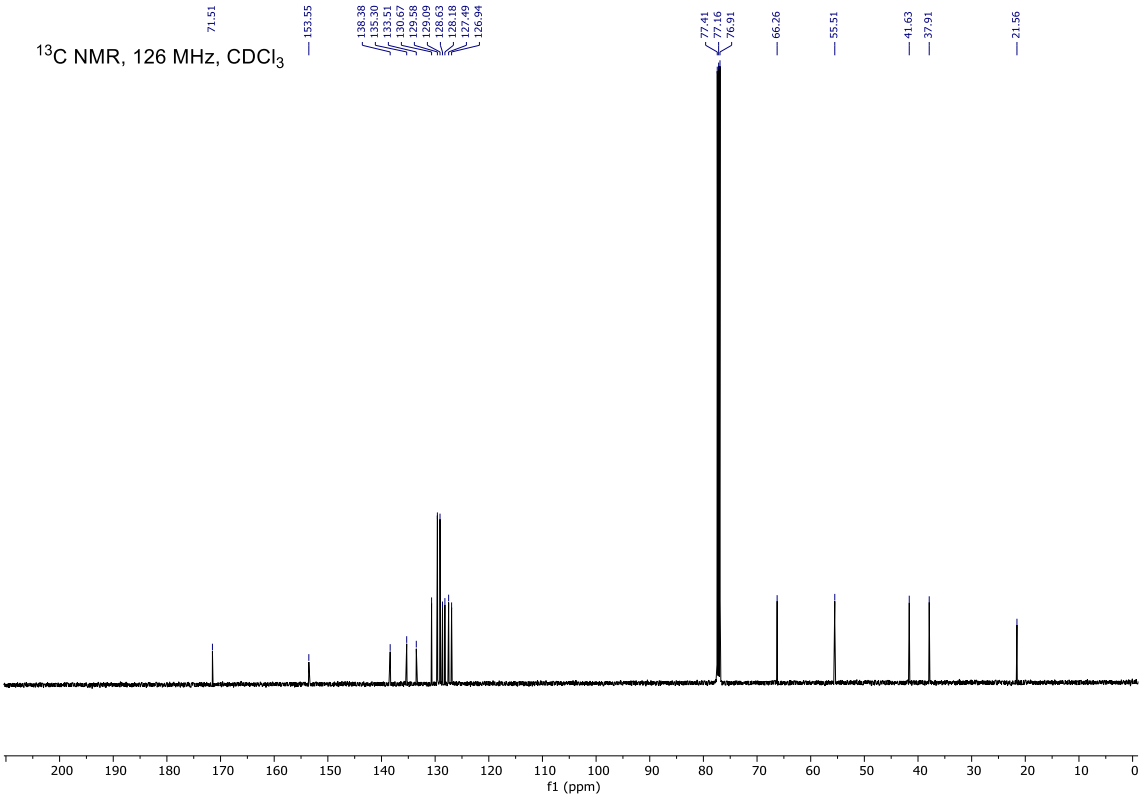
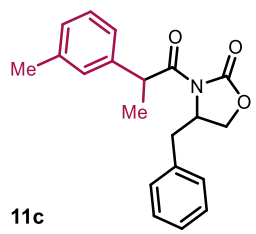
N. NMR Spectra



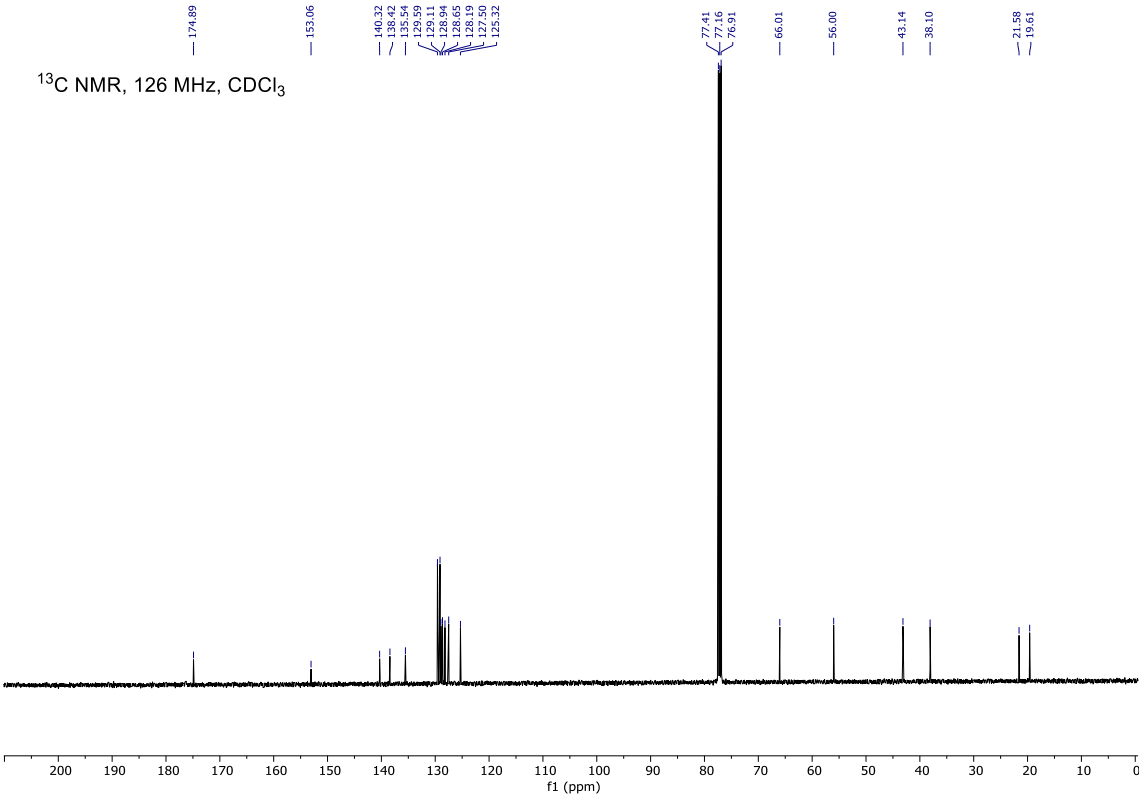


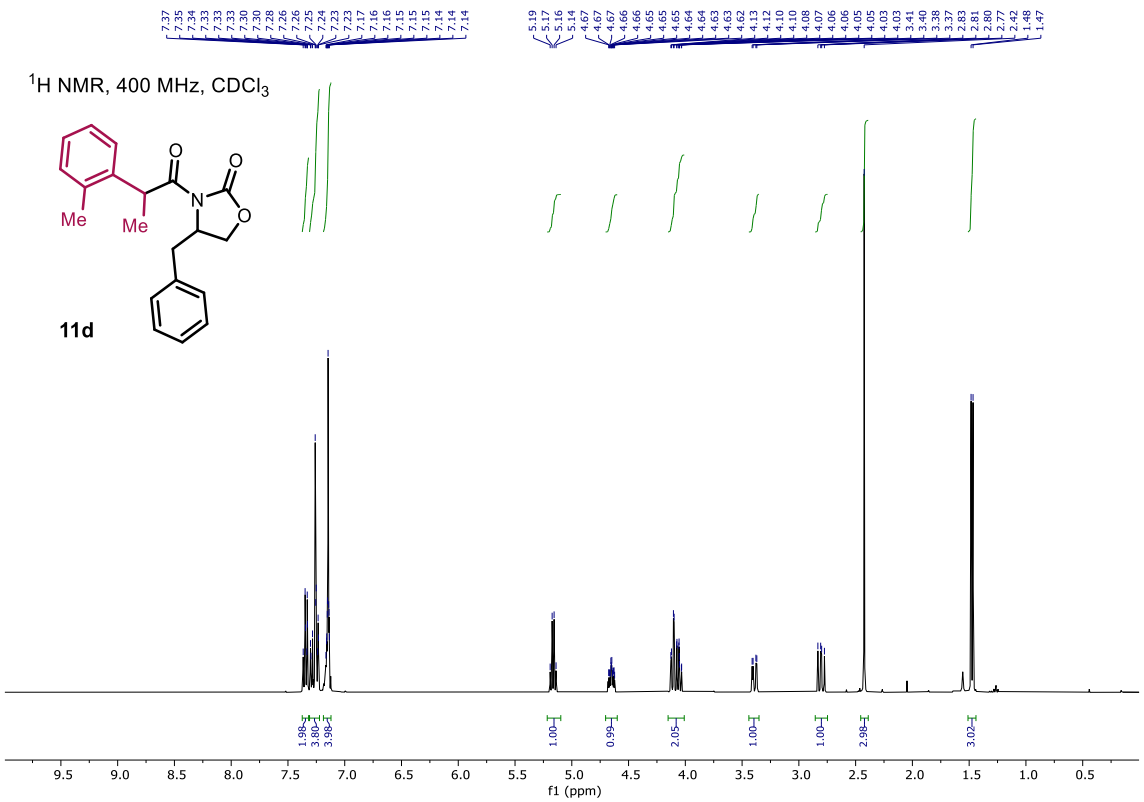
^{1}H NMR, 500 MHz, $CDCl_3$

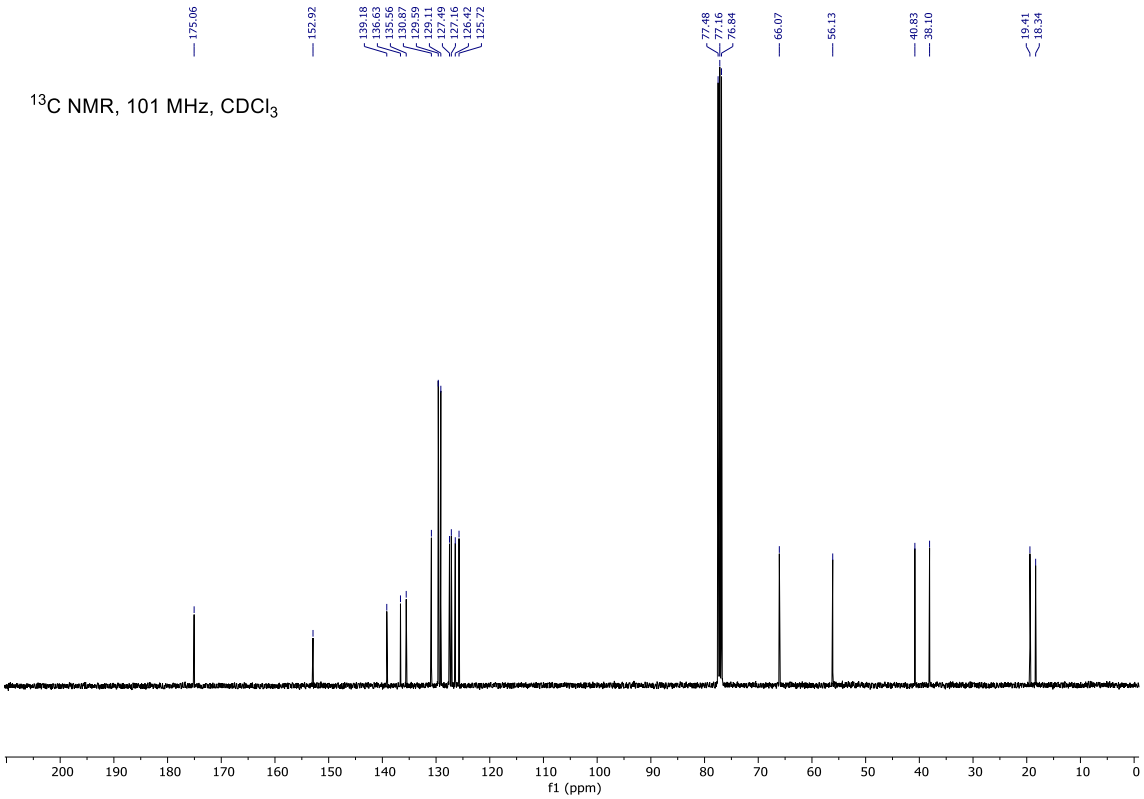


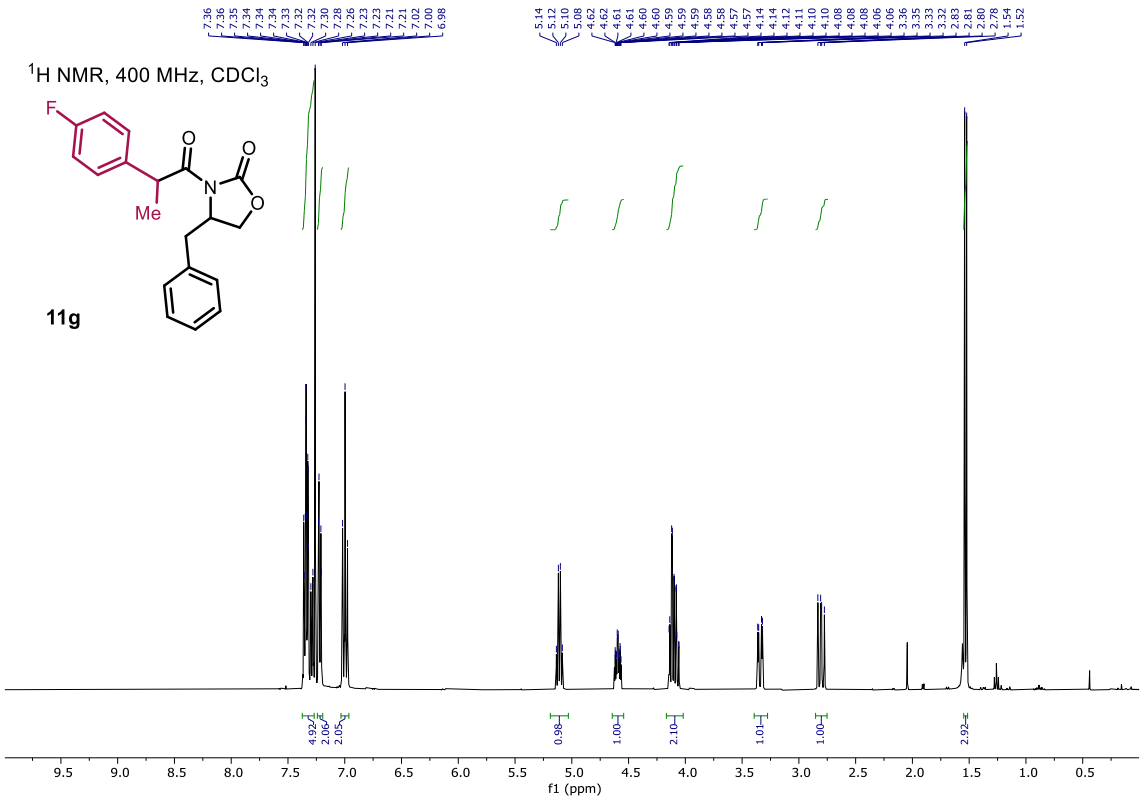
11c

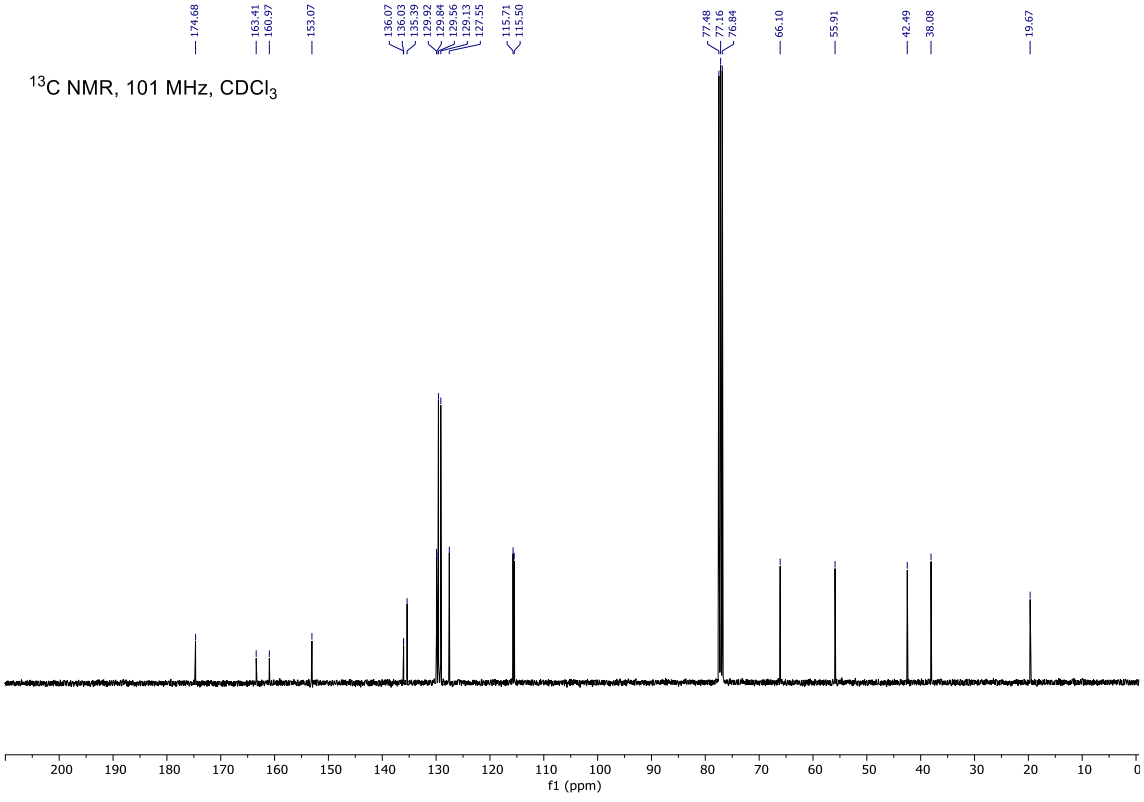
^{13}C NMR, 126 MHz, $CDCl_3$

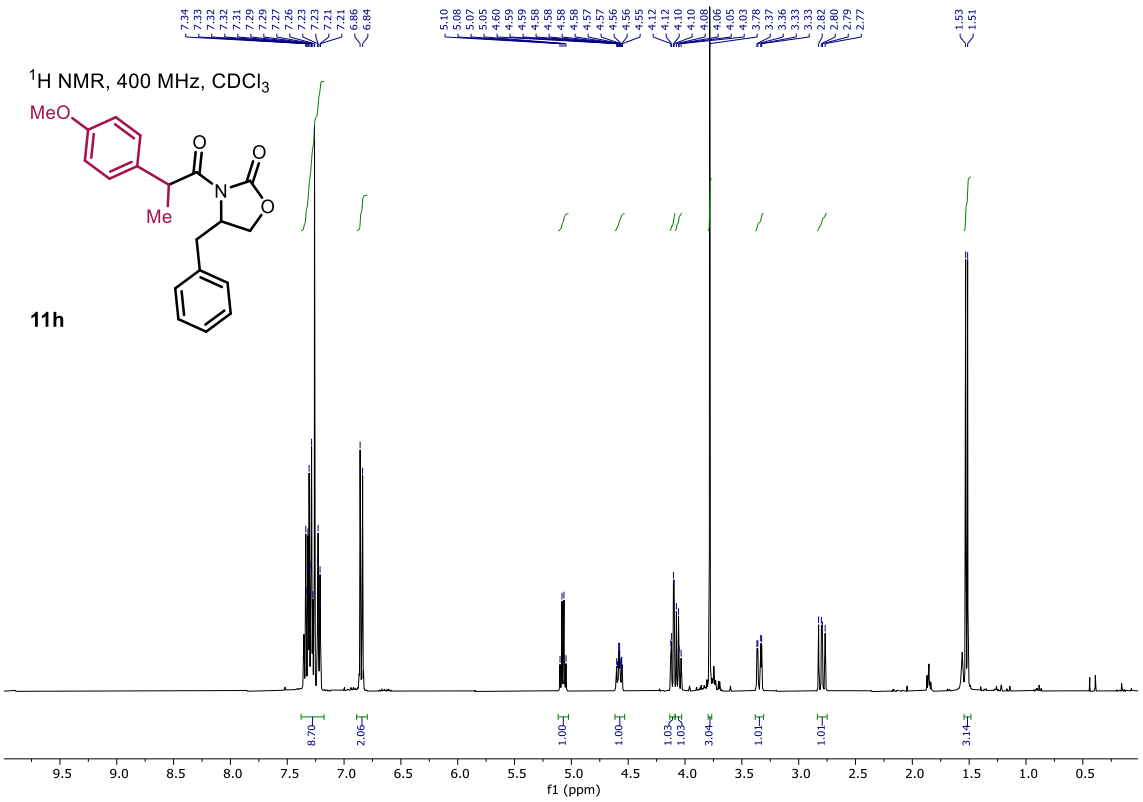


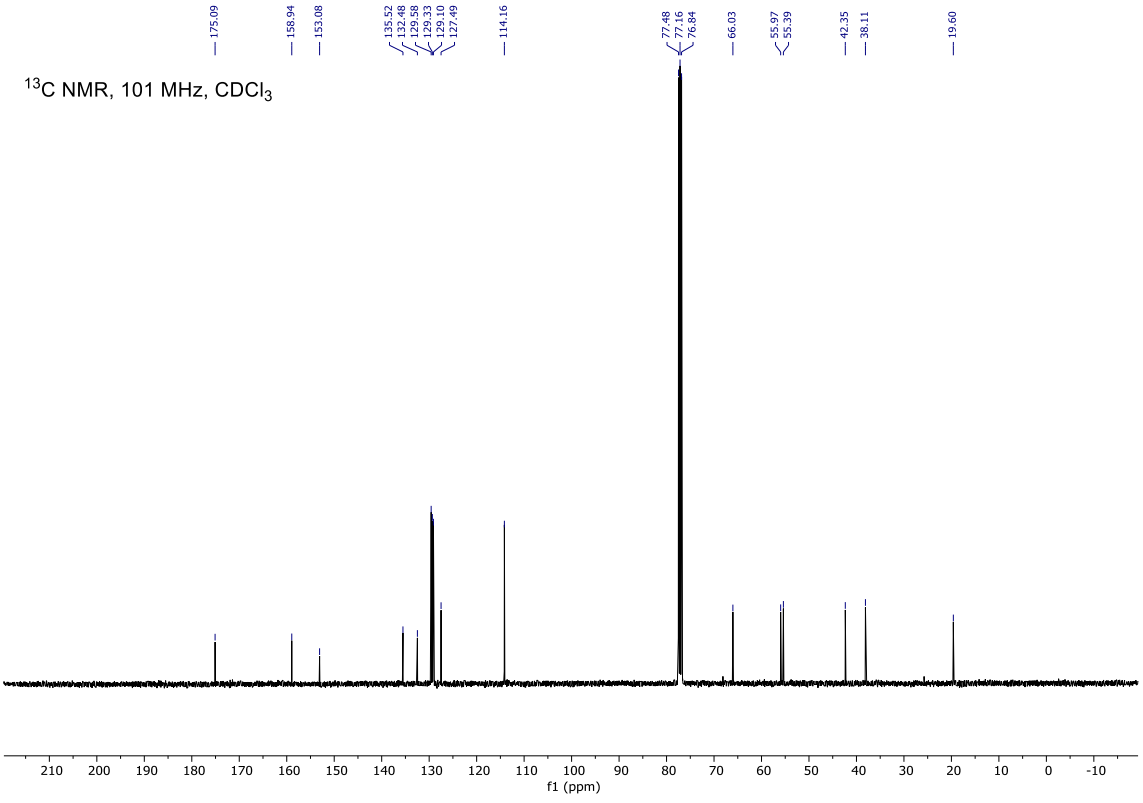

^{1}H NMR, 400 MHz, $CDCl_3$
Me
Me
O
O
N
O
11d
f1 (ppm)


^{13}C NMR, 101 MHz, $CDCl_3$
f1 (ppm)

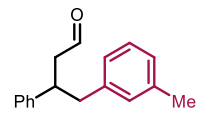

^{1}H NMR, 400 MHz, CDCl$_3$
F
O
O
N
O
Me
11g
f1 (ppm)


^{13}C NMR, 101 MHz, CDCl$_3$
f1 (ppm)


^{1}H NMR, 400 MHz, $CDCl_3$
MeO
Me
11h
f1 (ppm)

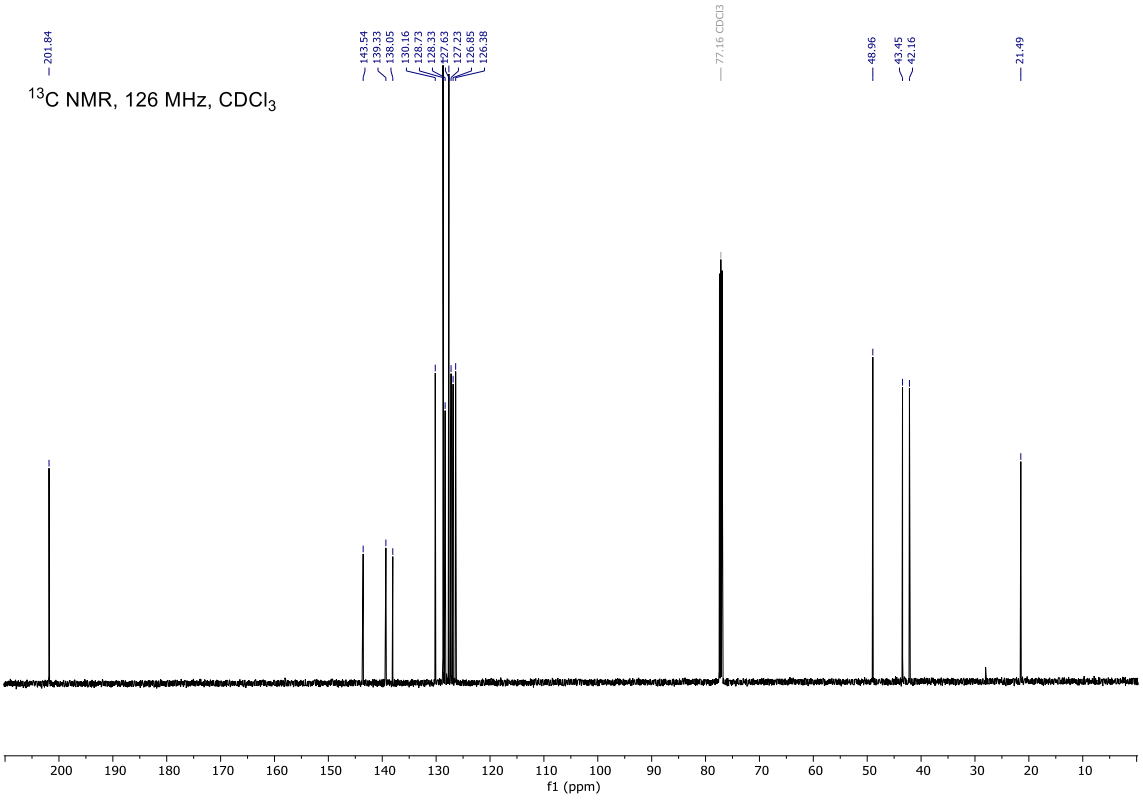

^{13}C NMR, 101 MHz, $CDCl_3$
f1 (ppm)

^{1}H NMR, 500 MHz, $CDCl_3$

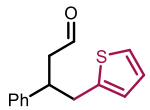


3c

^{13}C NMR, 126 MHz, $CDCl_3$

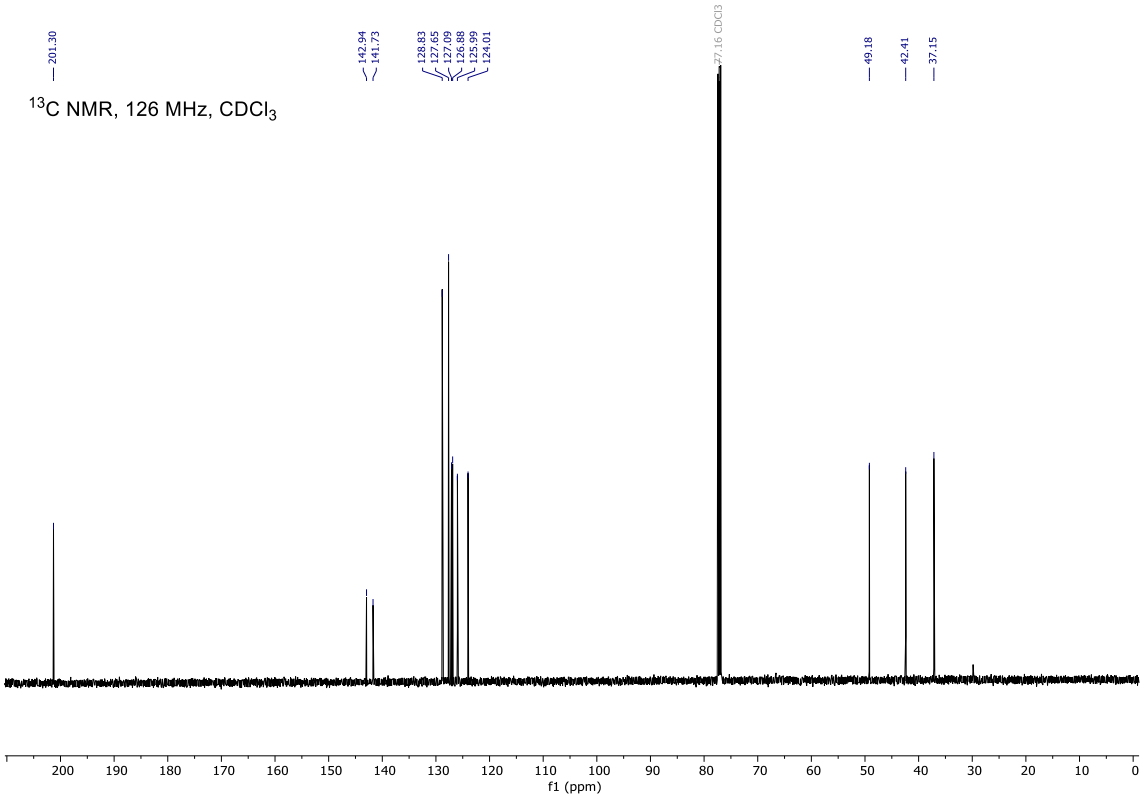


^{1}H NMR, 500 MHz, $CDCl_3$

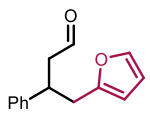


3i

^{13}C NMR, 126 MHz, $CDCl_3$

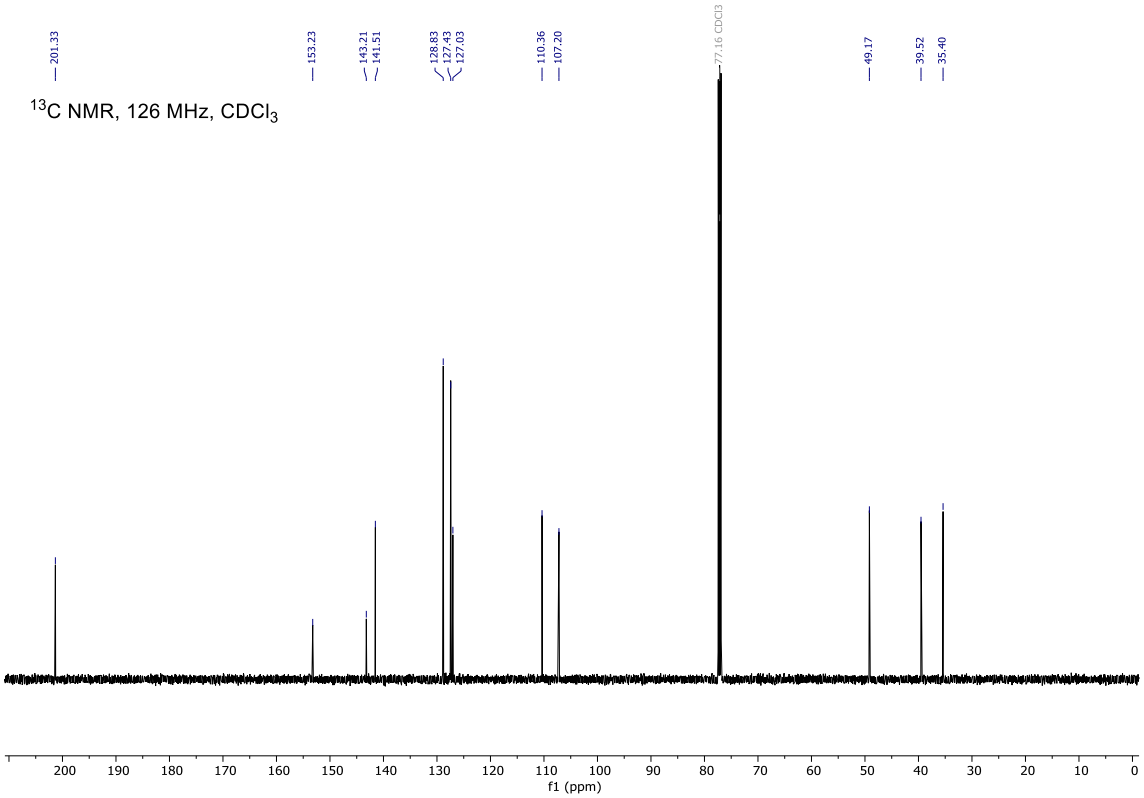


^{1}H NMR, 500 MHz, $CDCl_3$

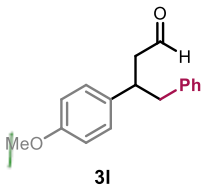


3j

^{13}C NMR, 126 MHz, $CDCl_3$

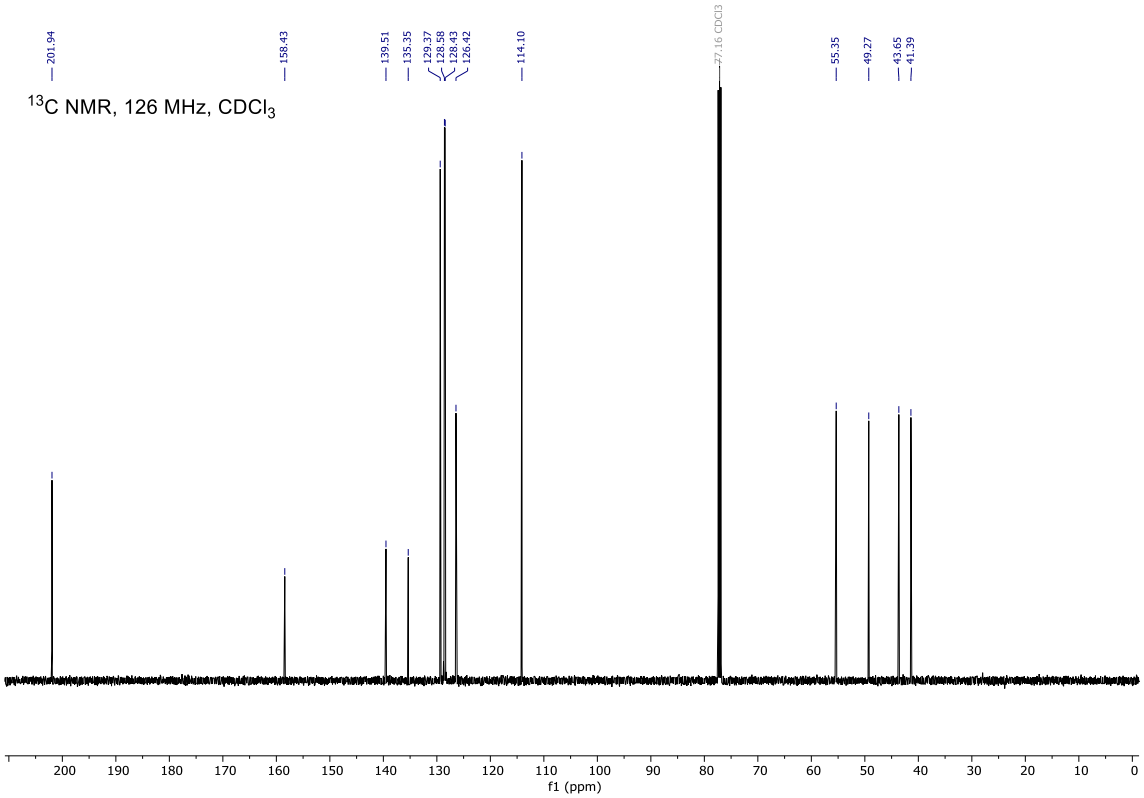


^{1}H NMR, 500 MHz, $CDCl_3$

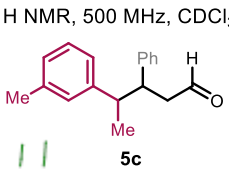


3l

^{13}C NMR, 126 MHz, $CDCl_3$

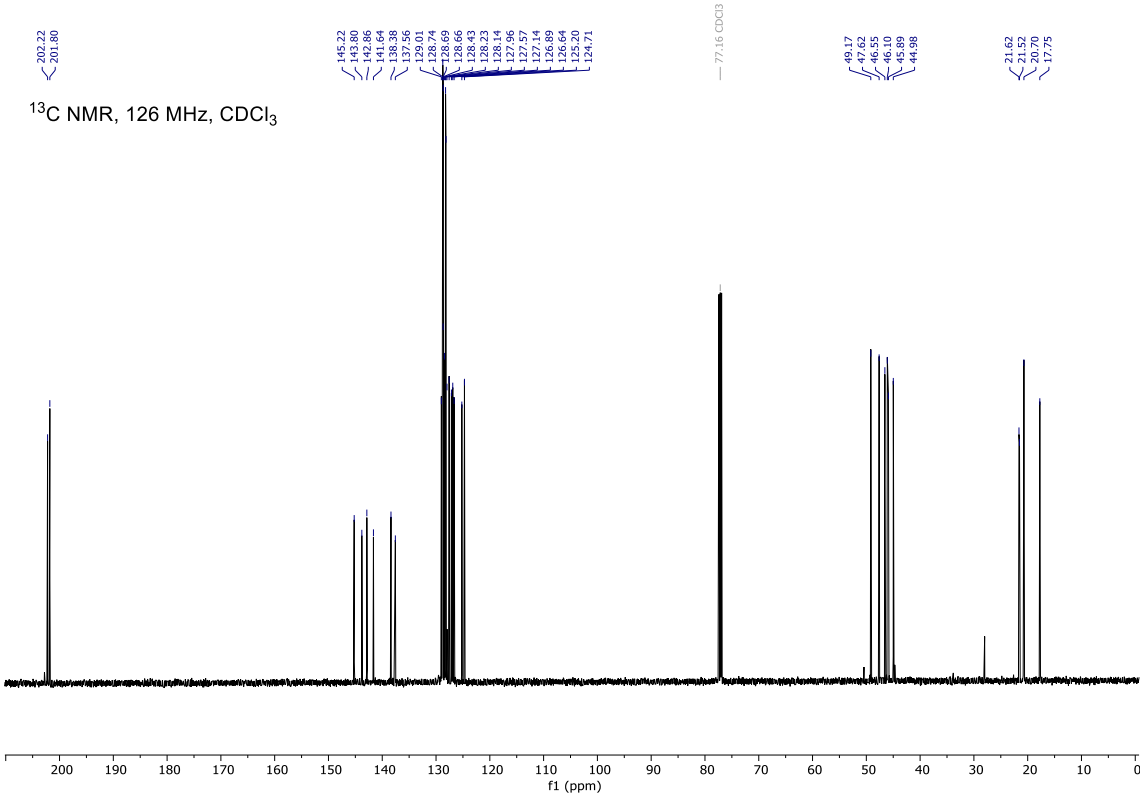


^{1}H NMR, 500 MHz, $CDCl_3$

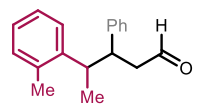


5c

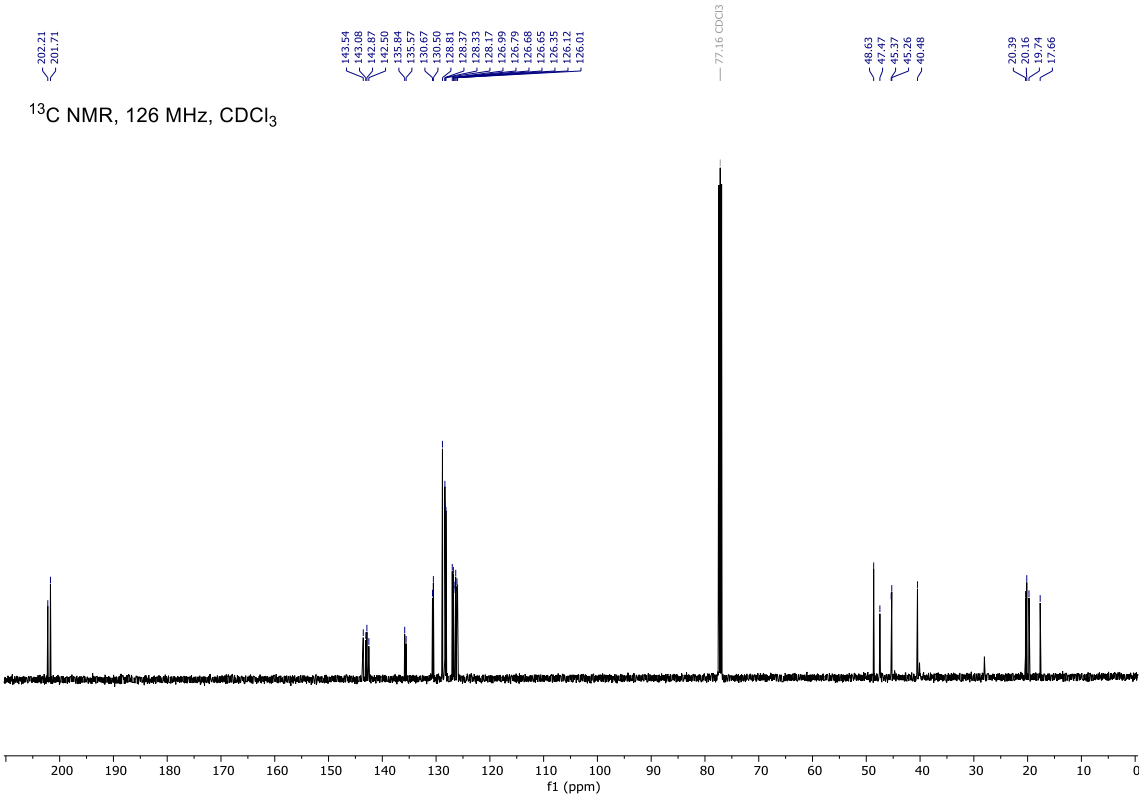
^{13}C NMR, 126 MHz, $CDCl_3$



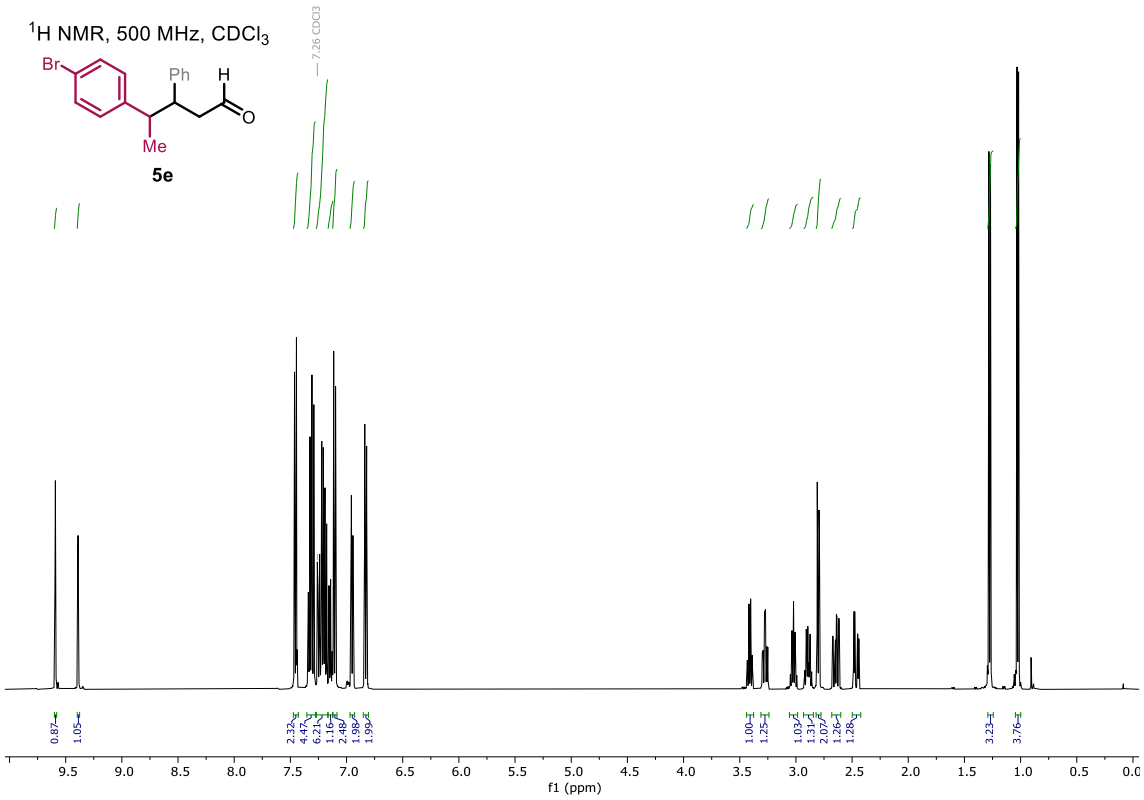
^{1}H NMR, 500 MHz, $CDCl_3$

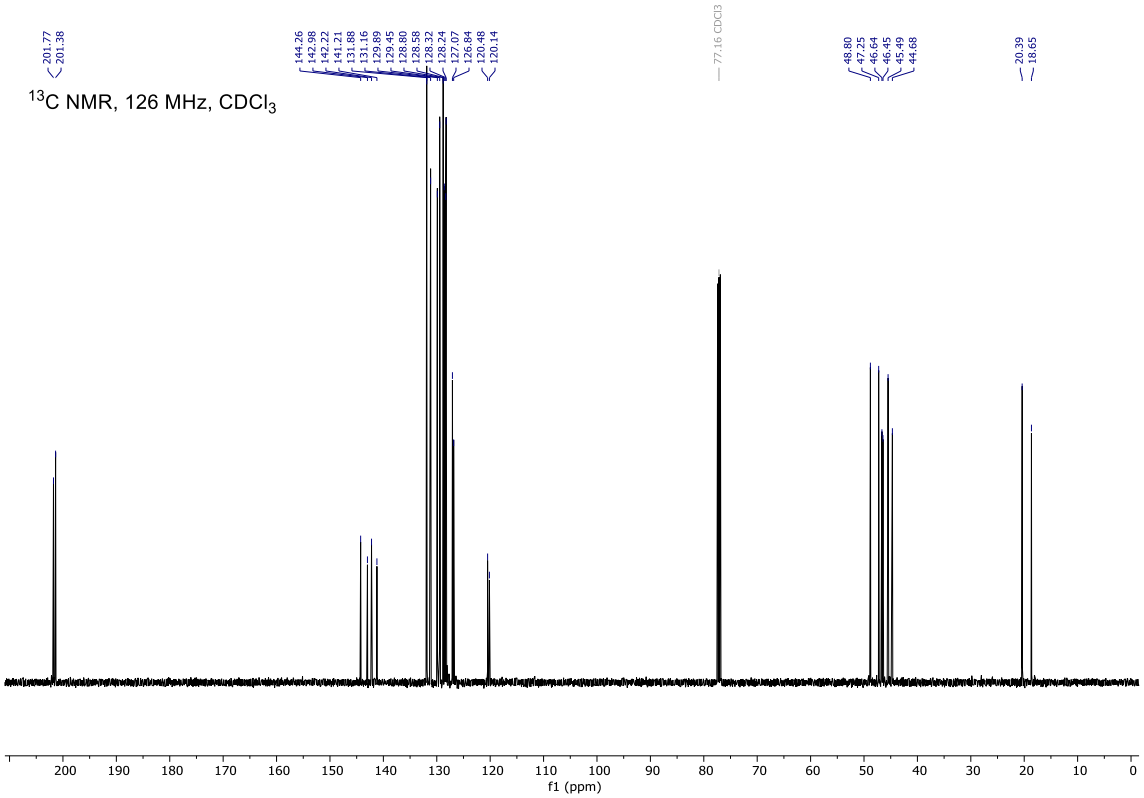


5d

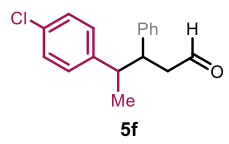


^{13}C NMR, 126 MHz, $CDCl_3$


1H NMR, 500 MHz, CDCl3
Br
Ph
H
O
Me
5e
7.26 CDCl3
0.87
1.05
2.32
4.47
6.21
1.16
2.48
1.98
1.99
1.00
1.25
1.03
1.31
2.07
1.26
1.28
3.23
3.76
f1 (ppm)

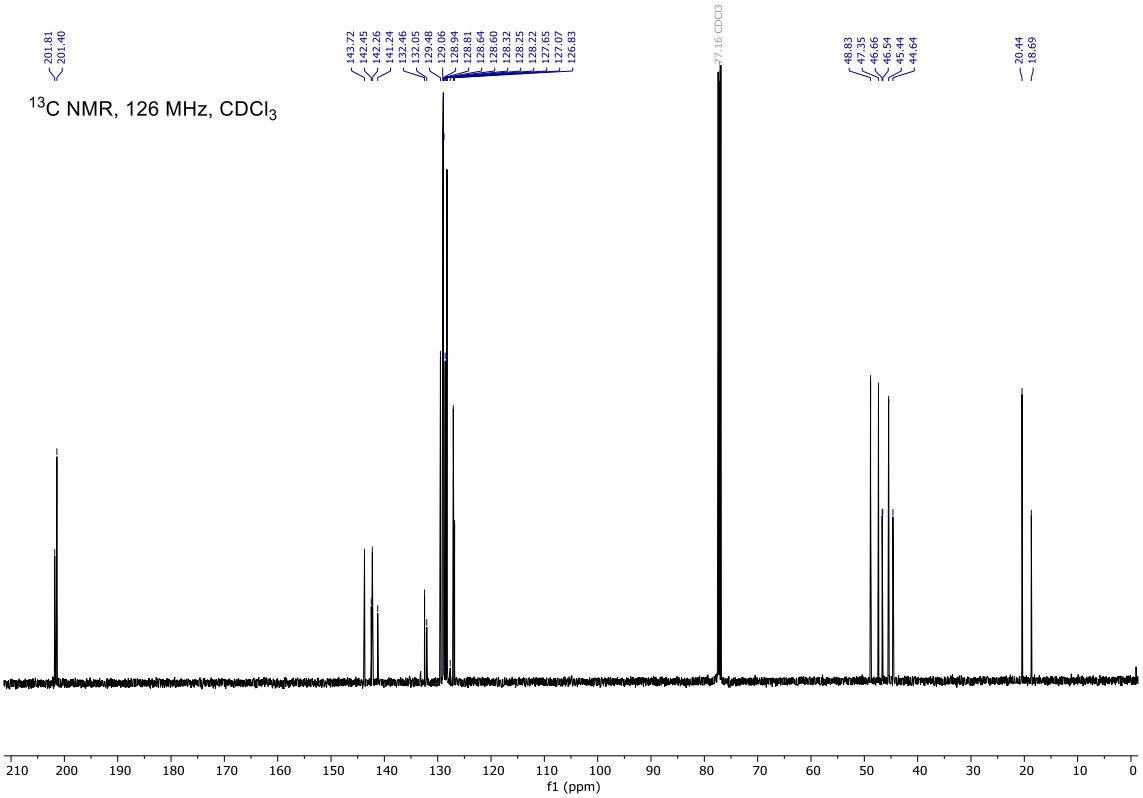

13C NMR, 126 MHz, CDCl3
201.77
201.38
144.26
142.98
142.22
141.71
131.88
131.16
129.89
129.45
128.80
128.58
128.32
128.24
127.07
126.84
120.48
120.14
77.16 CDCl3
48.80
47.25
46.64
46.45
45.49
44.68
20.39
18.65
f1 (ppm)

^{1}H NMR, 500 MHz, $CDCl_3$

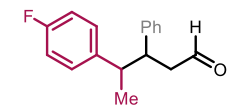


5f

^{13}C NMR, 126 MHz, $CDCl_3$

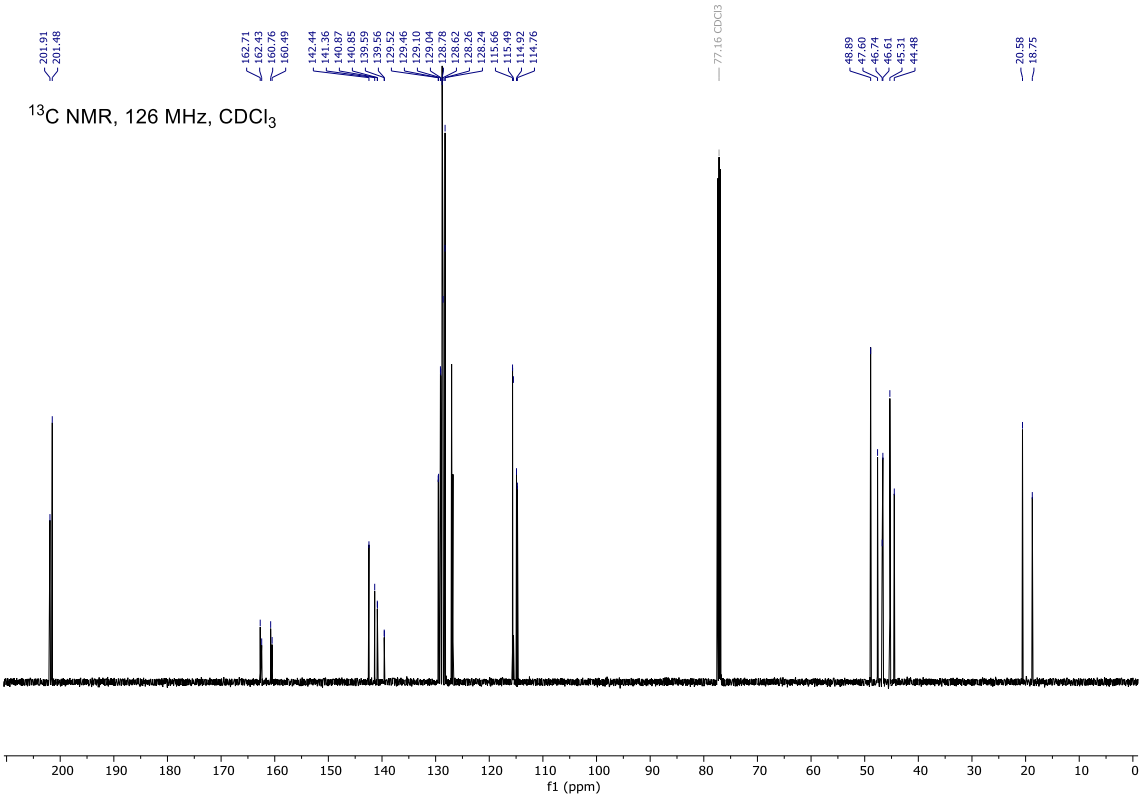


^{1}H NMR, 500 MHz, $CDCl_3$

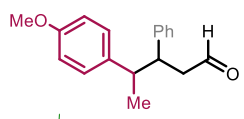


5g

^{13}C NMR, 126 MHz, $CDCl_3$

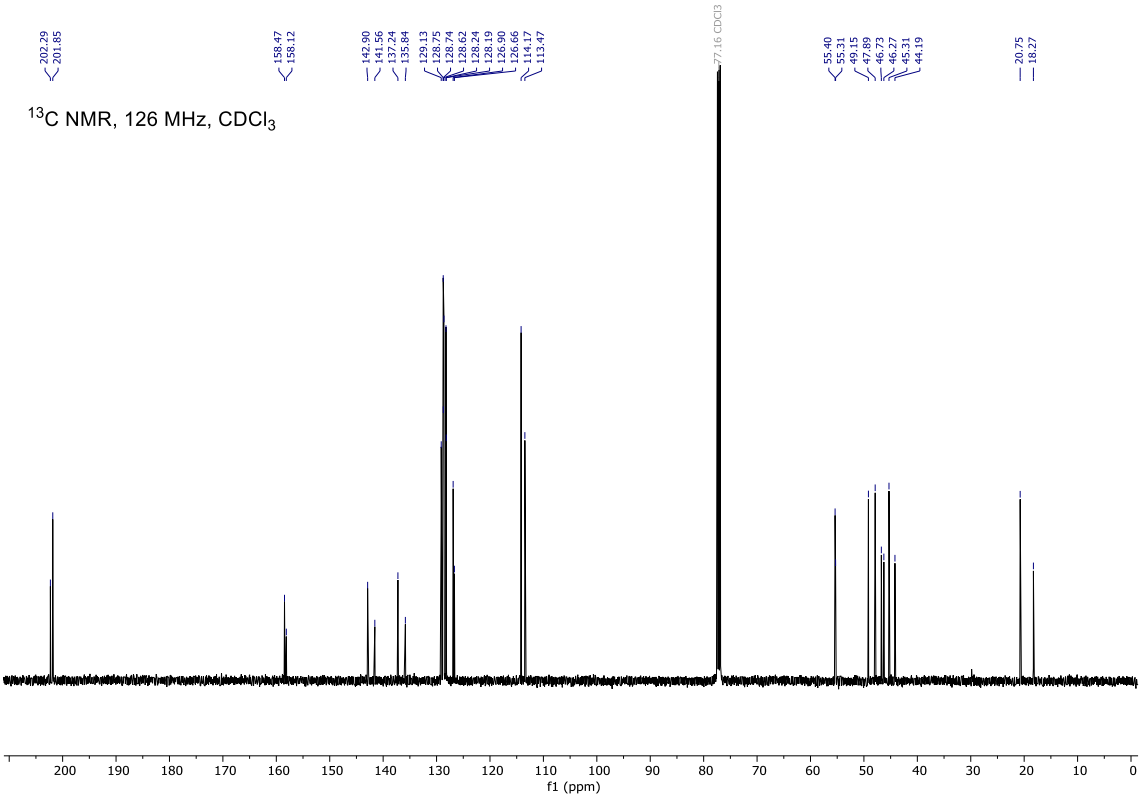


^{1}H NMR, 500 MHz, $CDCl_3$

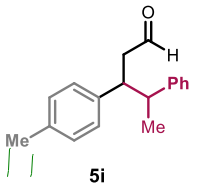


5h

^{13}C NMR, 126 MHz, $CDCl_3$

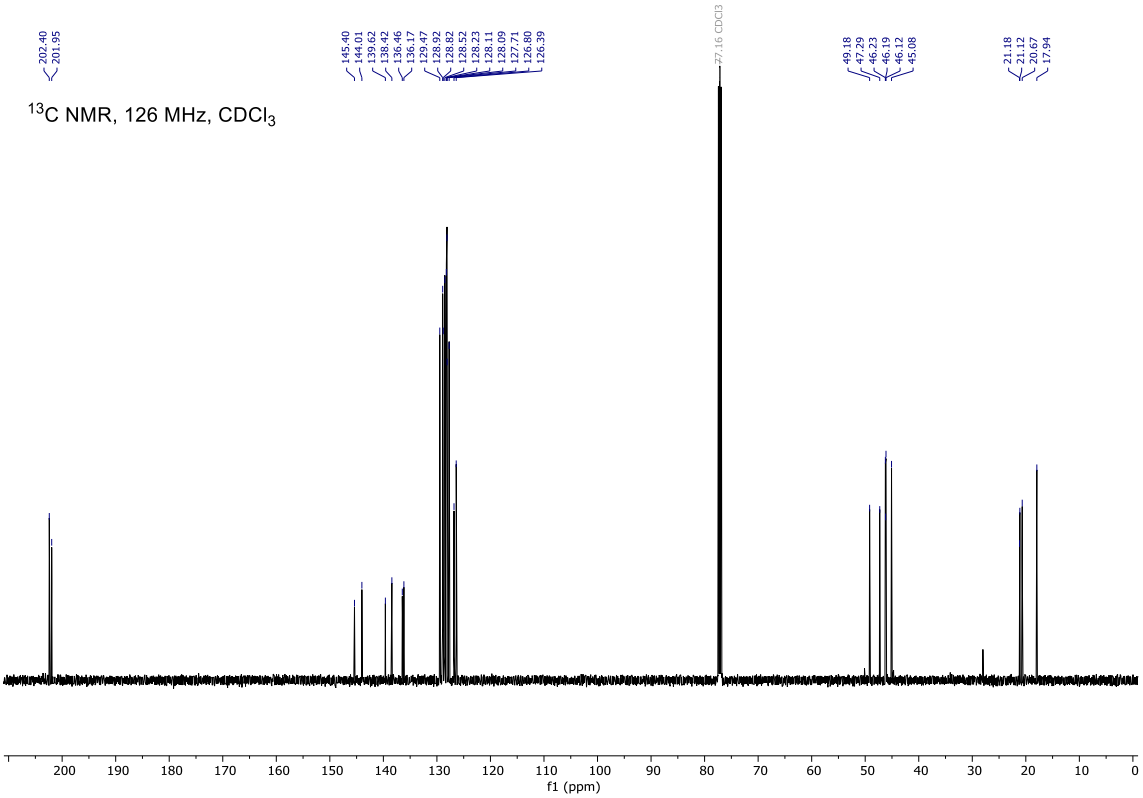


^{1}H NMR, 500 MHz, $CDCl_3$

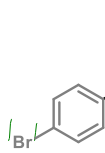


5i

^{13}C NMR, 126 MHz, $CDCl_3$

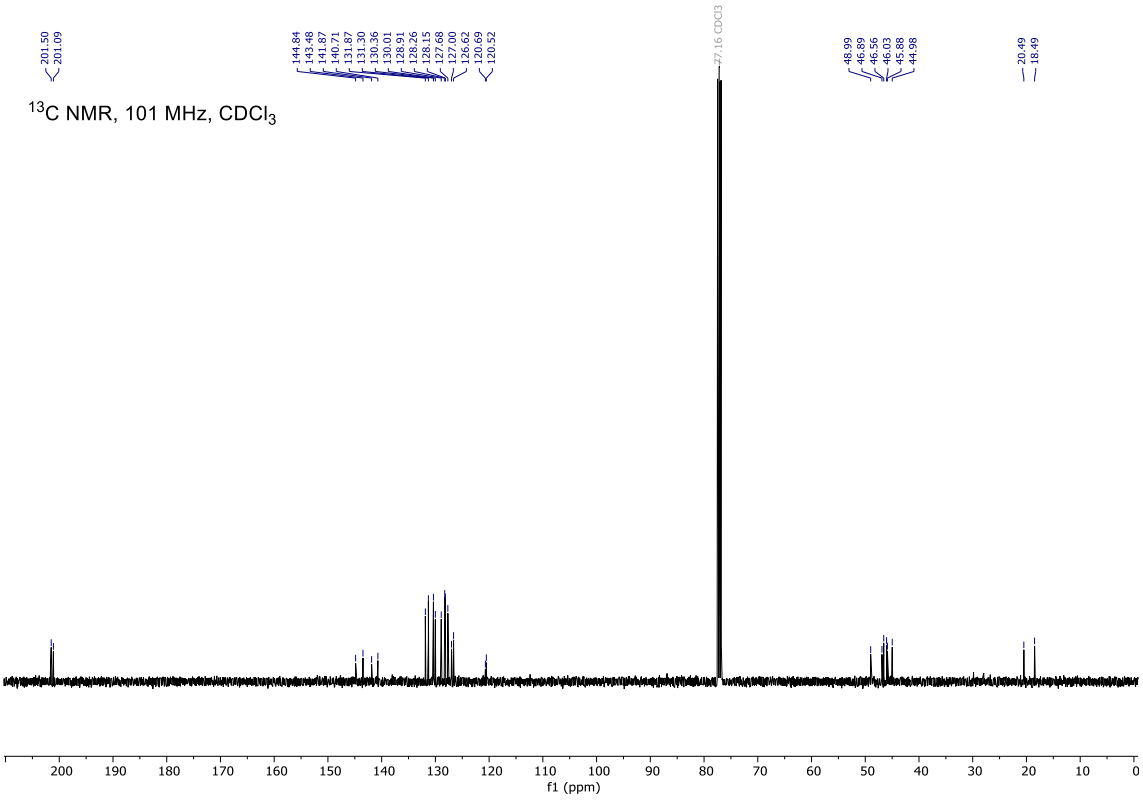


^{1}H NMR, 400 MHz, $CDCl_3$

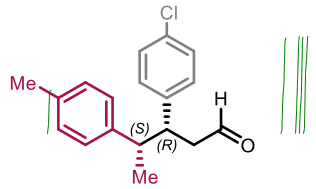


5j

^{13}C NMR, 101 MHz, $CDCl_3$

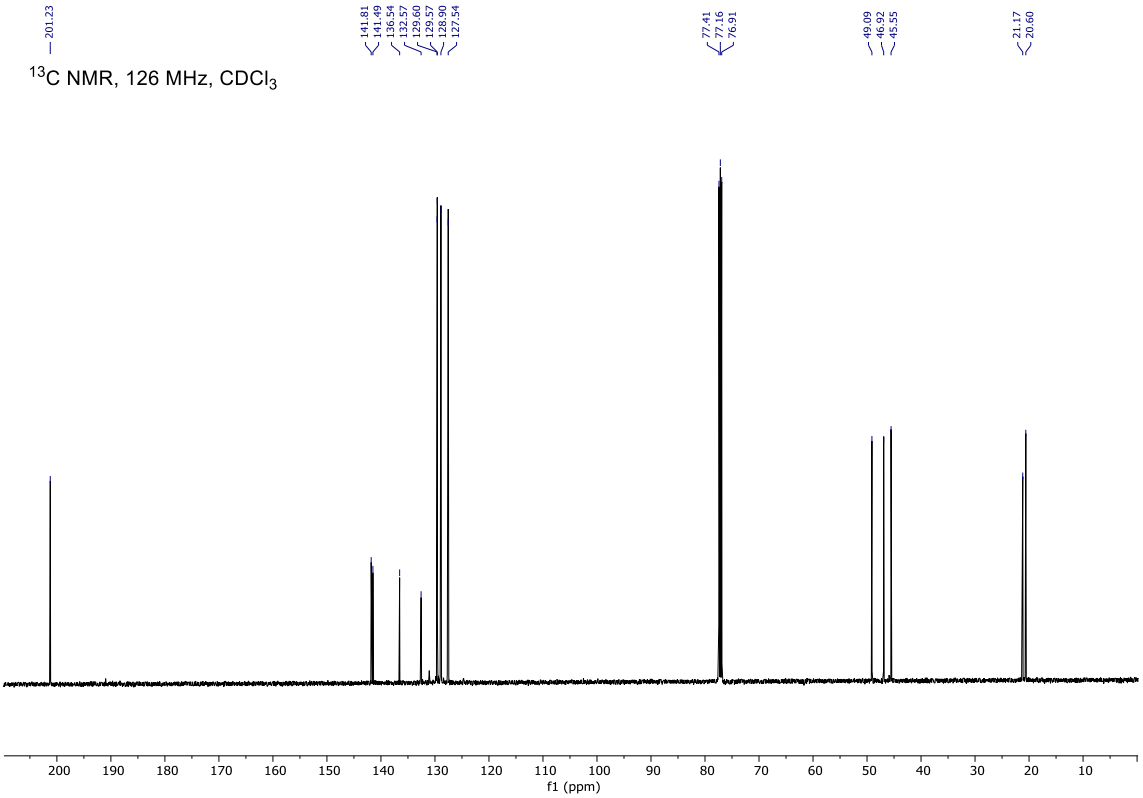


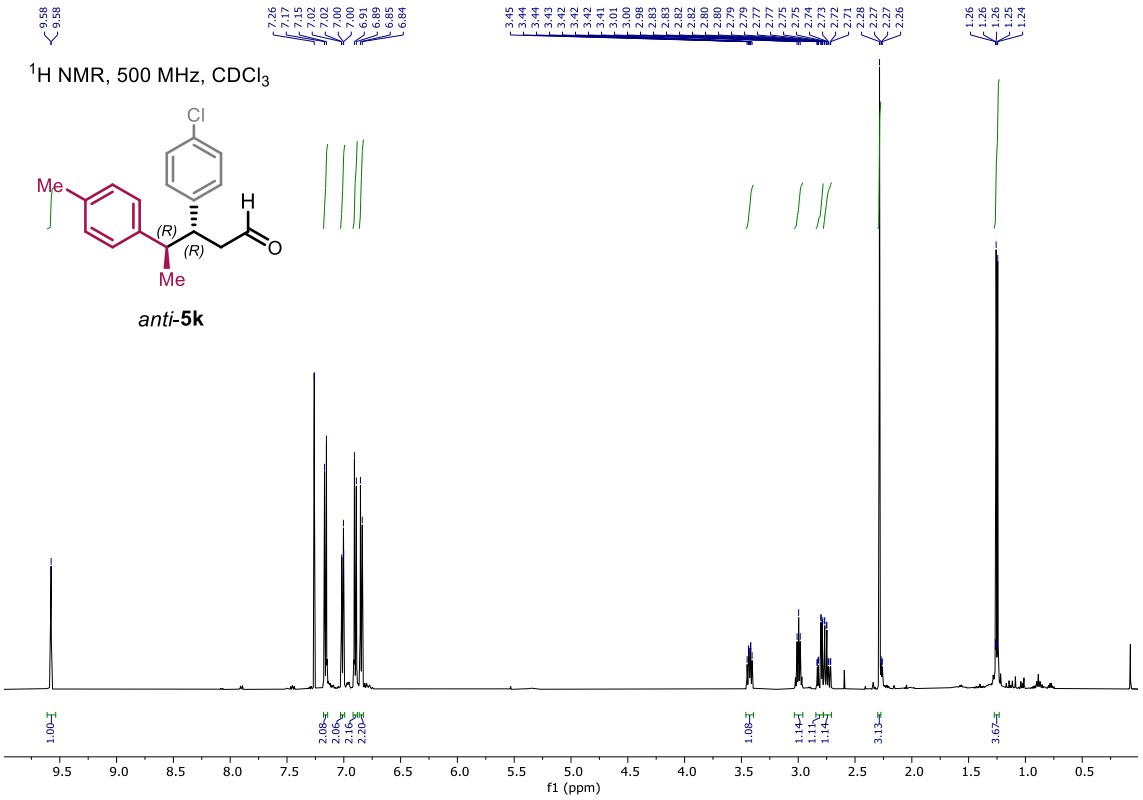
^{1}H NMR, 500 MHz, $CDCl_3$

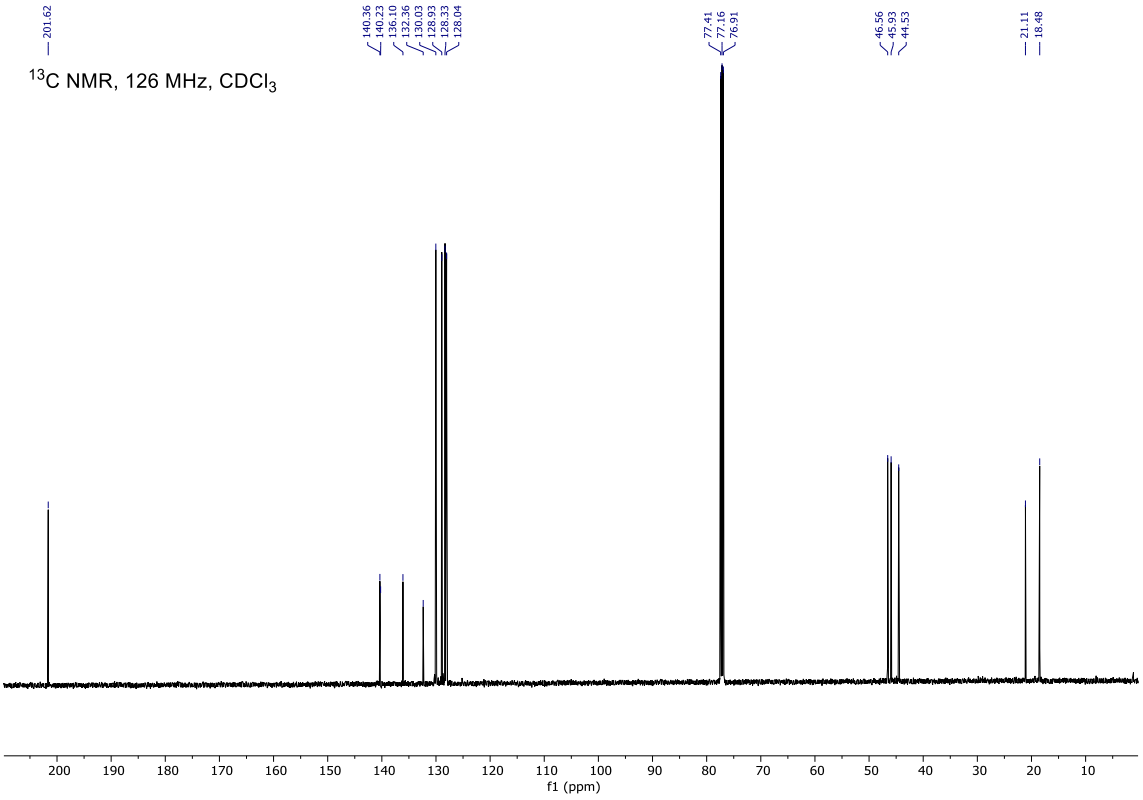


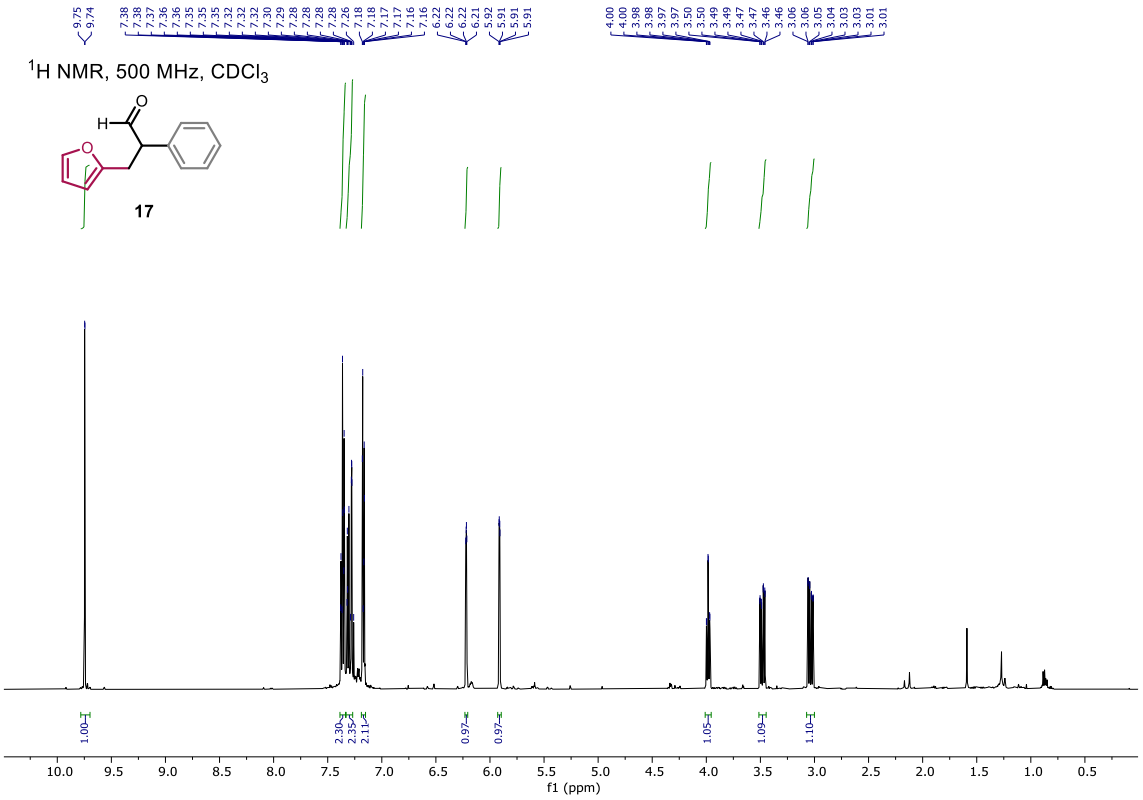
***syn*-5k**

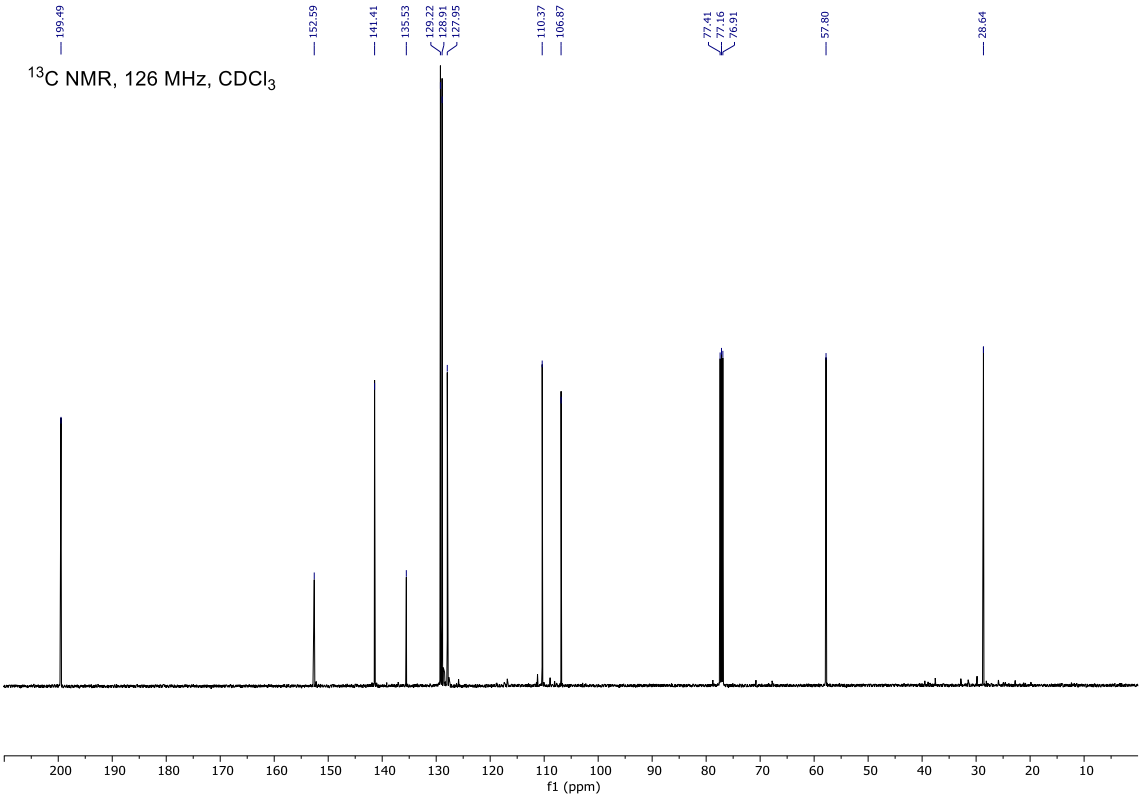
^{13}C NMR, 126 MHz, $CDCl_3$

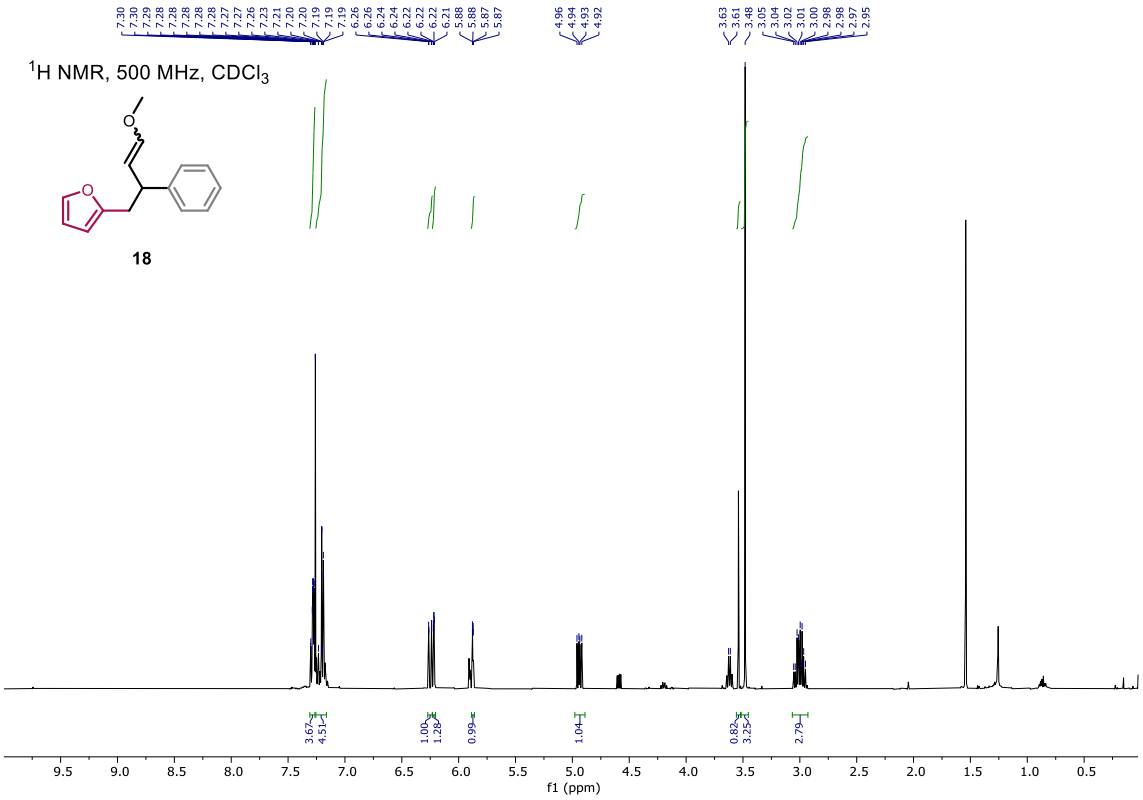


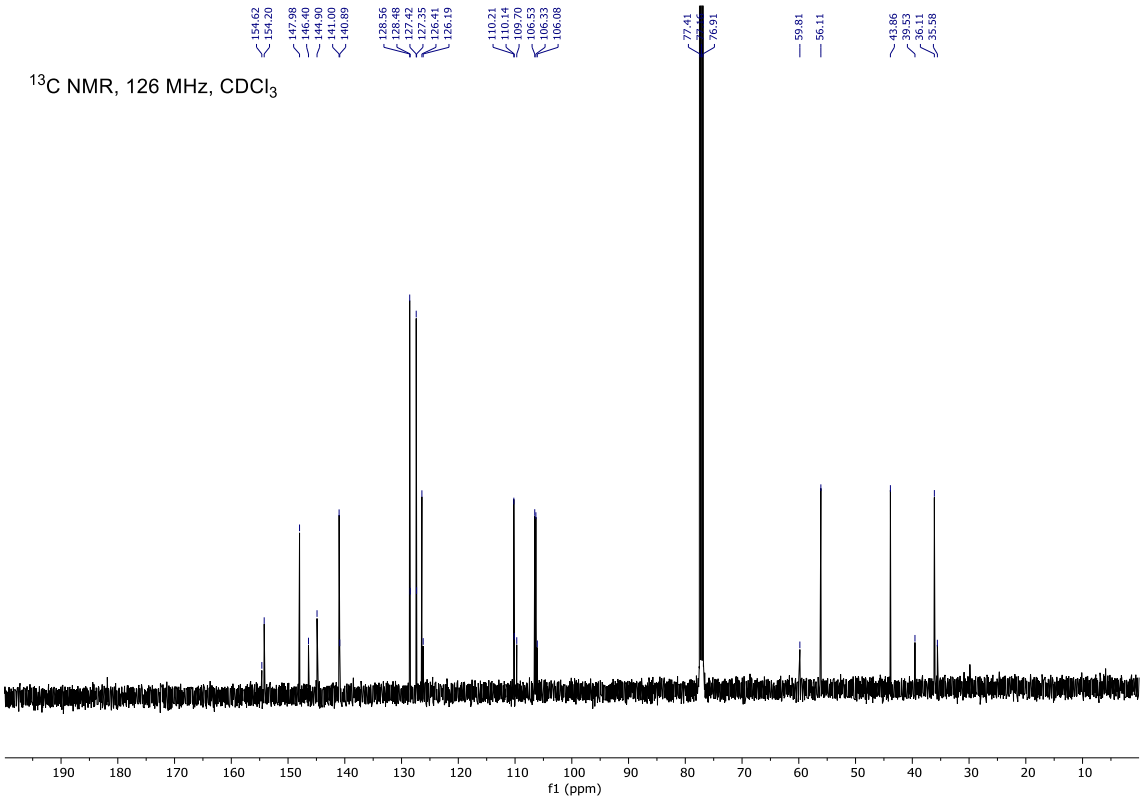

9.58
9.58
7.26
7.17
7.15
7.02
7.02
7.00
7.00
6.91
6.89
6.85
6.84
3.45
3.44
3.44
3.43
3.42
3.42
3.41
3.01
3.00
2.98
2.83
2.82
2.82
2.80
2.80
2.79
2.79
2.77
2.77
2.75
2.75
2.74
2.73
2.72
2.71
2.28
2.27
2.27
2.26
1.26
1.26
1.26
1.25
1.24
1H NMR, 500 MHz, CDCl3
Cl
Me
H
(R)
(R)
O
Me
anti-5k
1.00
2.08
2.06
2.16
2.20
1.08
1.14
1.11
1.14
3.13
3.67
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


201.62
140.36
140.23
135.10
132.36
130.03
128.93
128.33
128.04
77.41
77.16
76.91
46.56
45.93
44.53
21.11
18.48
13C NMR, 126 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

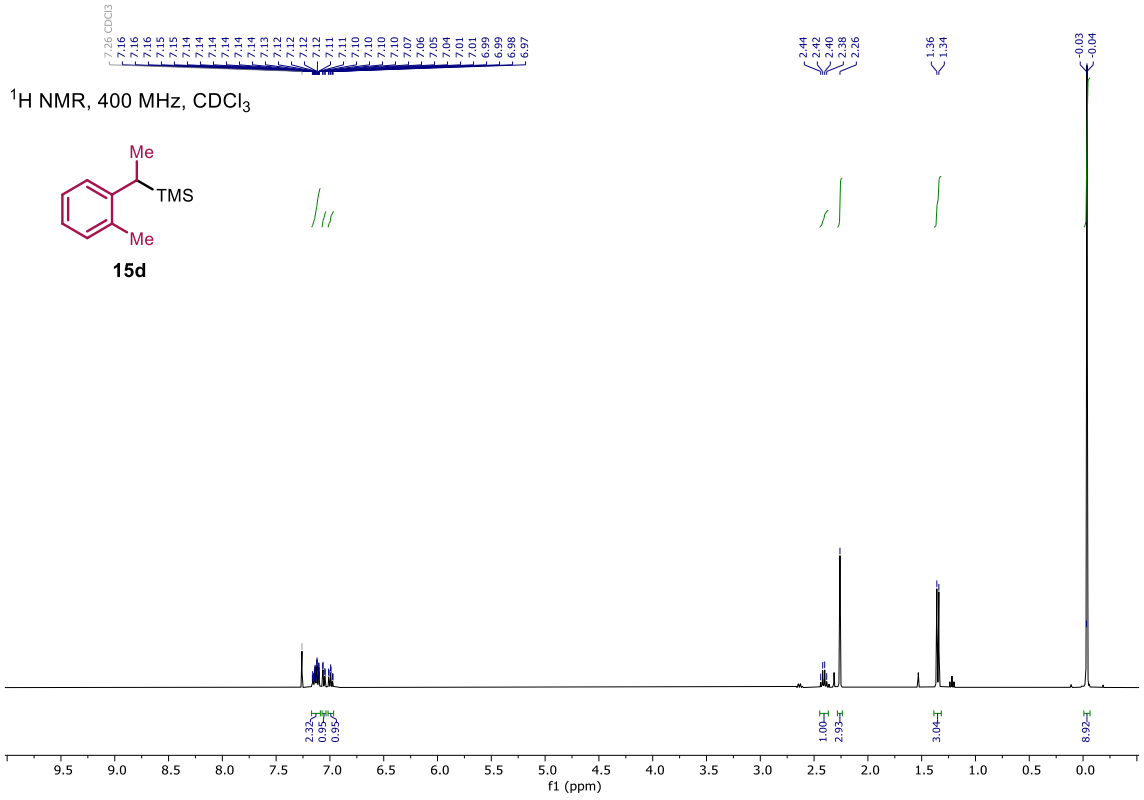

^{1}H NMR, 500 MHz, $CDCl_3$
17
f1 (ppm)

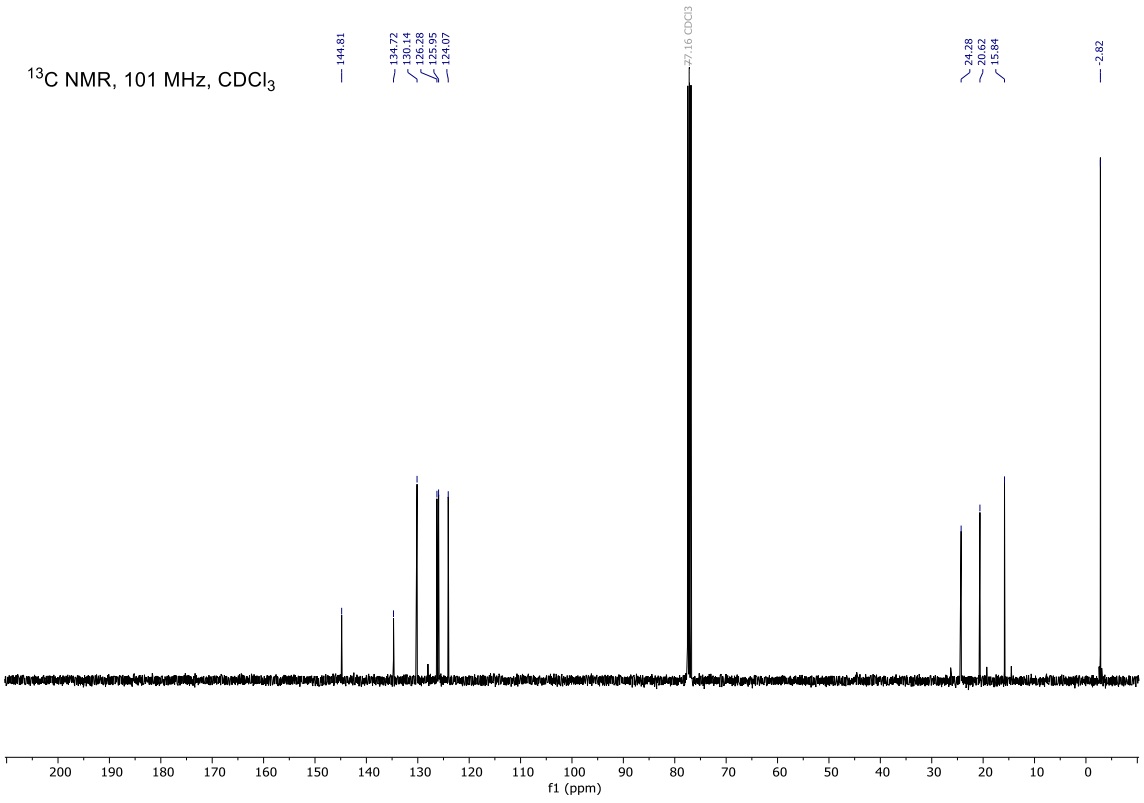

^{13}C NMR, 126 MHz, $CDCl_3$
f1 (ppm)


1H NMR, 500 MHz, CDCl3
18
f1 (ppm)

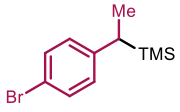

13C NMR, 126 MHz, CDCl3
f1 (ppm)

L.3 NMR Spectra of Silanes 15



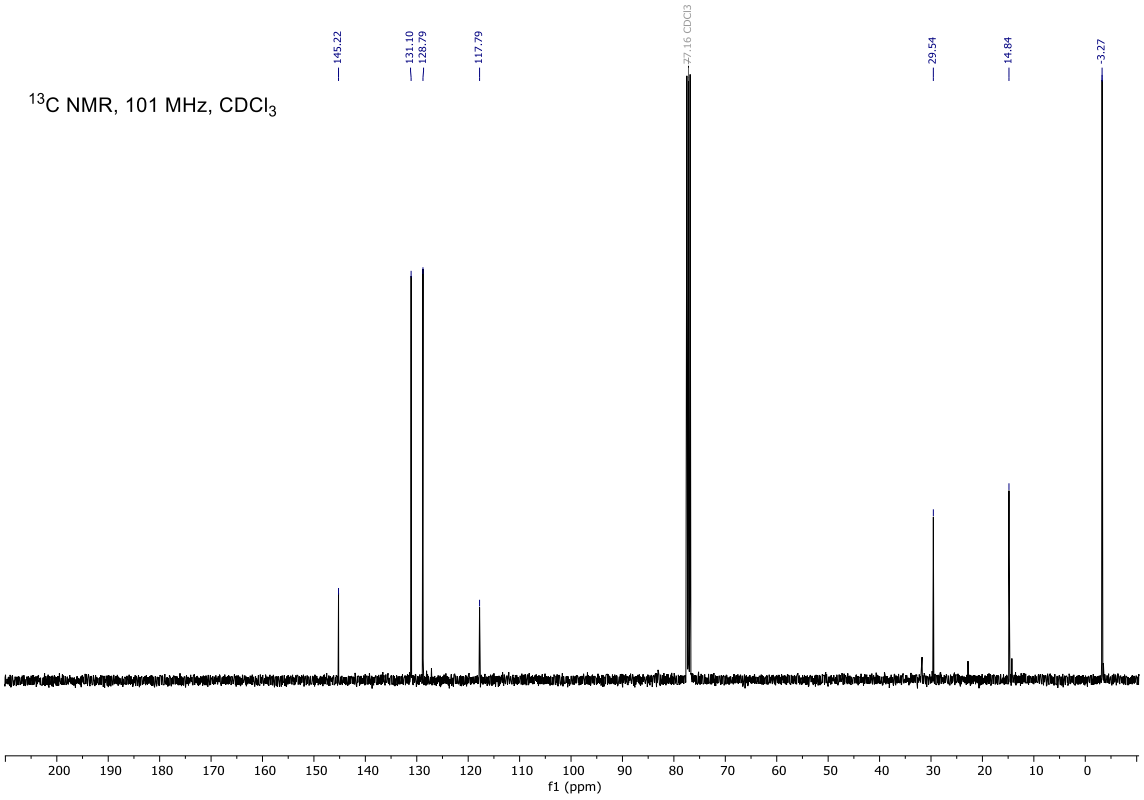


^{1}H NMR, 400 MHz, $CDCl_3$

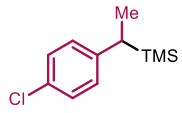


15e

^{13}C NMR, 101 MHz, $CDCl_3$

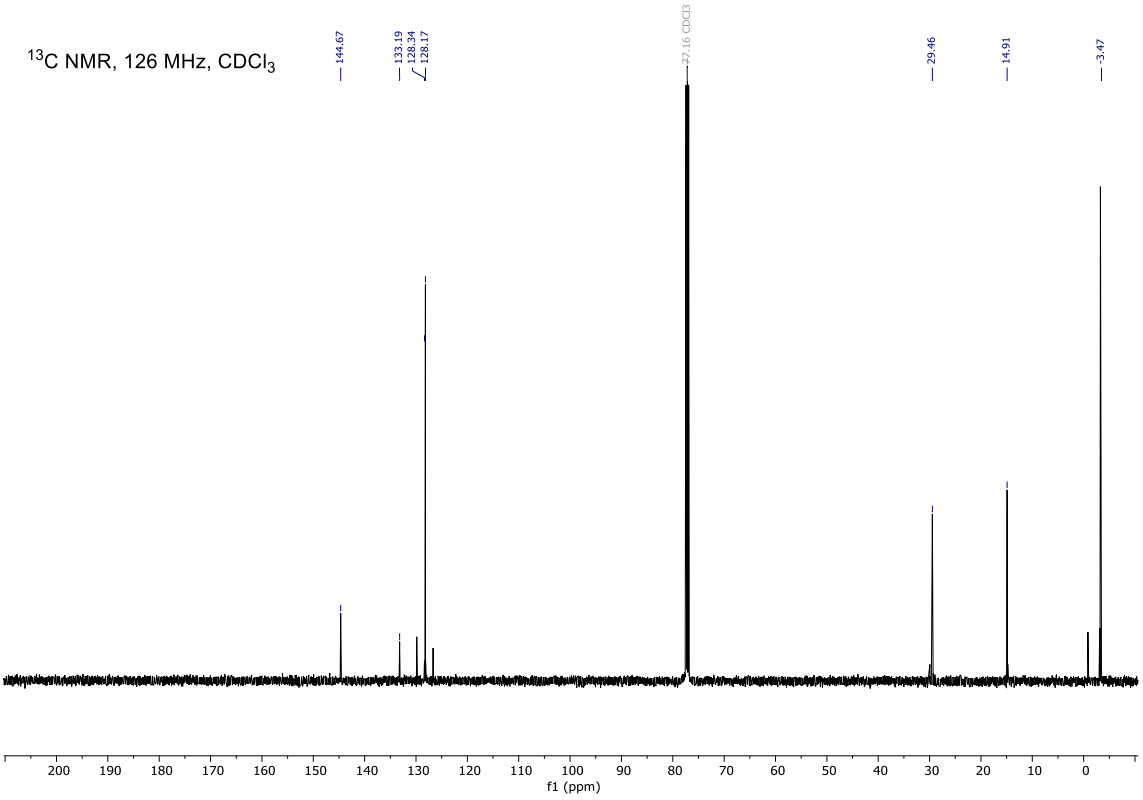


^{1}H NMR, 500 MHz, $CDCl_3$

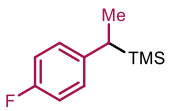


15f

^{13}C NMR, 126 MHz, $CDCl_3$



^{1}H NMR, 500 MHz, $CDCl_3$



15g

^{13}C NMR, 126 MHz, $CDCl_3$