Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

Dynamic Kinetic Resolution Allows Control of Remote Stereochemistry in Asymmetric Hydrogen Borrowing Alkylation

D. M. J. Cheang, J. L. Crompton, M. M. Amer, F. Battiti, B. B. Skjelstad, K. E. Christensen, P. Barton, F. Duarte, T. J. Donohoe**

Dynamic kinetic resolution allows control of remote stereochemistry in asymmetric hydrogen borrowing alkylation: Supporting Information

Daniella M. J. Cheang,[a] Jessica L. Crompton,[a] Mostafa M. Amer,[a] Francisco Battiti,[a] Bastian Bjerkem Skjelstad,[a] Kirsten E. Christensen,[a¥] Peter Barton,[b] Fernanda Duarte, *[a§] and Timothy J. Donohoe*[a]

[a] Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford, OX1 3TA (UK)
E-mail: timothy.donohoe@chem.ox.ac.uk

[b] Oncology R&D, AstraZeneca, 1 Francis Crick Avenue, Cambridge Biomedical Campus, Cambridge, CB2 0AA (UK).

1. GENERAL INFORMATION S2

2. GENERAL PROCEDURES S4

3. OPTIMISATION S6

4. PREPARATION AND CHARACTERISATION OF COMPOUNDS S11

4.1 Synthesis of linear alcohol precursors S11

4.2 Hydrogen Borrowing Cyclisations S26

4.3 Synthesis of diols S37

4.4 Mechanistic Experiments S39

4.5 Derivatisation of Hydrogen Borrowing Products S41

5. **REFERENCES**

6. X-RAY CRYSTALLOGRAPHY DATA S46

7. COMPUTATIONAL DATA S51

1. General Information

Reactions were carried out in flame-dried glassware under an atmosphere of nitrogen unless stated otherwise. Room temperature (r.t.) refers to 20-25 °C. Temperatures of 0 °C were obtained using an ice/water bath. Temperatures of –17 °C were obtained using a salt/ice bath. Temperatures of –78 °C were obtained using a dry ice/acetone bath. Heating was achieved using an oil bath equipped with a contact thermometer.

Diethyl ether, CH_2Cl_2 and tetrahydrofuran were purified by filtration through activated alumina columns employing the method of Grubbs *et al*.[1] All other solvents and reagents were used as supplied without prior purification. All other reagents were used directly as supplied by major chemical suppliers. Potassium *tert*-butoxide, sublimed grade, 99.99% trace metals basis, was purchased from Sigma Aldrich.

Thin layer chromatography was performed on Merck Kieselgel 60 F_{254} 0.25 mm pre-coated aluminium plates. Product spots were visualized under UV light (λ = 254 nm) and/or by staining with potassium permanganate solution. Flash chromatography was performed using VWR silica gel 60 (40-63 μm particle size) using head pressure by means of a nitrogen line.

NMR spectroscopy was carried out using a Bruker 400 MHz spectrometer in the deuterated solvent stated, using the residual non-deuterated solvent signal as an internal reference. Chemical shifts are quoted in ppm with signal splittings recorded as singlet (s), doublet (d), triplet (t), quartet (q), quintet (qn), sextet (sext), septet (sept), octet (oct), nonet (non) and multiplet (m). The abbreviation br denotes broad. Coupling constants, *J*, are measured to the nearest 0.1 Hz and are presented as observed.

Infrared spectra were recorded neat on a Bruker Tensor 27 spectrometer equipped with an attenuated total reflectance attachment with internal calibration. Absorption maxima (λ_{max}) are quoted in wavenumbers (cm^{-1}). The abbreviation br denotes broad.

Electrospray ionisation (ESI) HRMS were recorded on a Thermo Exactive orbitrap spectrometer equipped with a Waters Equity LC system, with a flow rate of 0.2 mL/min using water:methanol:formic acid (10:89.9:0.1) as eluent. The system uses a heated electrospray ionisation (HESI-II) probe for ESI^+ and has a resolution of 50,000 FWHM under conditions for maximum sensitivity, with an accuracy of better than 5 ppm for 24 h following external calibration on the day of analysis. The mass reported is that containing the most abundant isotopes, with each value rounded to 4 decimal places and within 5 ppm of the calculated mass. Electron impact ionisation (EI) HRMS were performed on an Agilent 7200 quadrupole time of flight (Q-ToF) instrument equipped with a direct insertion probe supplied by Scientific Instrument Manufacturer (SIM) GmbH. Instrument control and data processing were performed using Agilent MassHunter software. The mass reported is that containing the most abundant isotopes, with each value to 4 decimal places and within 5 ppm of the calculated mass.

Optical rotations were recorded on a Schmidt Haensch Unipol L2000 polarimeter in a cell with a path length of 1 dm (using the sodium D line, 589 nm). Concentrations are reported in g/100 mL. Temperatures are reported in °C.

Chiral normal phase HPLC was performed on an Agilent 1260 Series HPLC unit equipped with UV-vis diode-array detector, fitted with the appropriate Daicel Chiralpak column (dimensions: 0.46 cm ø x 25 cm) along with the corresponding guard column (0.4 cm ø x 1 cm). Wavelengths (λ) are reported in nm, retention times (t_R) are reported in minutes and solvent flow rates are reported in mL min^{-1}.

Reverse phase HPLC was performed on a Dionex UltiMate 3000 system equipped with UV-vis variable wavelength detector, fitted with an Agilent InfinityLab Poroshell 120 EC-C18 column (0.46 cm ø x 150 mm, 4 µm pore size).

Single crystal X-ray diffraction data were collected using a Rigaku Synergy-DW diffractometer (EP/V028995/1) and CrysAlisPro. In all cases, Cu-Kα (λ = 1.54184 Å) radiation was used and the instrument was equipped with a nitrogen gas Oxford Cryosystems Cryostream unit. Data were collected at 100 K. Structures were solved using 'Superflip'[2] before refinement with CRYSTALS[3, 4] as per the SI (CIF).

2. General procedures

General procedure A: Hydrogen borrowing alkylation of linear alcohols.

To a 2 – 5 mL Biotage® microwave vial equipped with a stirrer bar was added the appropriate linear alcohol (0.30 mmol, 1.0 equiv.), chiral ligand (5.0 mol%), Ir(cod)acac (4.0 mol%) and KO^{t}Bu (0.6 mmol, 2.0 equiv.) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum), then evacuated and backfilled with nitrogen. ^{t}BuOH (0.5 mL, 0.6 M) was purged with nitrogen for 15 min, added to the reaction vessel and stirred at 110 °C in a preheated oil bath for 18 h. [If the linear alcohols were oil instead of solids, and the reaction mixture was additionally sparged with Ar for 5 min after the addition of solvent and then heated to 110 °C.] The mixture was cooled to r.t., diluted with Et_2O, filtered through a SiO_2 plug (eluting with ca. 50 mL Et_2O), concentrated and purified by column chromatography (see experimental methods section for details). Purification generally required the use of Merck Silica gel 60 (15 – 40 µm). Racemic cyclohexane products were obtained using our previously reported procedure.[2]

General procedure B: Hydrogen borrowing annulation using 1,5-diols.

To a 2 – 5 mL Biotage® microwave vial equipped with a stirrer bar was added the appropriate diol (0.30 mmol, 1.0 equiv.), pentamethylacetophenone **1** (0.60 mmol, 2.0 equiv.), chiral ligand (5.0 mol%), Ir(cod)acac (4.0 mol%) and KO^{t}Bu (0.6 mmol, 2.0 equiv.) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum), then evacuated and backfilled with nitrogen. ^{t}BuOH (0.1 mL, 3 M) was purged with nitrogen for 15 min, added to the reaction vessel and stirred at 110 °C in a preheated oil bath for 18 h. The mixture was cooled to r.t., filtered through a SiO_2 plug (eluting with ca. 50 mL Et_2O). For ease of purification from residual (*R*)-DTBM-SEGPHOS, a solution of the crude product in Et_2O (ca. 40 mL) was treated with *tert*-butyl hydroperoxide (5-6 M in decane, 50 µL, ~0.28 mmol), swirled and allowed to stand at r.t. for 10 min. The resulting solution was then concentrated and purified by column chromatography (see experimental methods section for details). Racemic cyclohexane products were obtained using a previously reported procedure.[33]

General procedure C: Alkylation of Ph* malonates.

Cs_2CO_3 (13.2 mmol, 1.20 equiv.) was added to a solution of the appropriate malonate (11.0 mmol, 1.00 equiv.) in DMF (90 mL) and stirred for 15 min at r.t. The appropriate alkyl halide (44.0 mmol, 4.00 equiv.) was added and the resulting mixture was stirred overnight at r.t. to 80 °C (see experimental methods section for details). The reaction mixture was quenched with sat. aq. NH_4Cl (60 mL) and extracted with Et_2O (3 × 60 mL). The combined organic extracts were washed with aqueous LiCl (5 wt%, 3 × 50 mL), brine (3 × 50 mL), and dried ($MgSO_4$). The resulting solution was then concentrated and purified by column chromatography (see experimental methods section for details).

General procedure D: Decarboxylation of Ph* malonates.

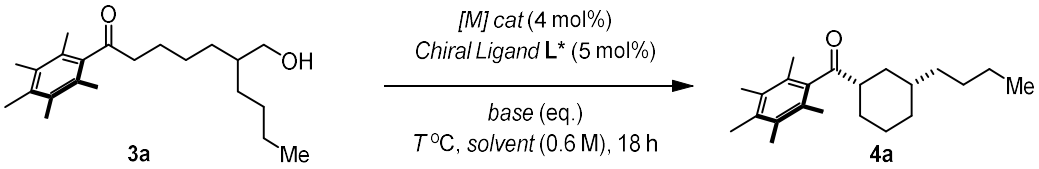
The appropriate malonate (1.00 equiv.) was added to a solution of LiCl (3.00 equiv.) in H_2O and DMSO. The resulting reaction mixture was stirred at 160 °C and monitored by TLC (see experimental methods section for details). The reaction mixture was cooled and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (see experimental methods section for details).

General procedure E: Reduction of Ph* esters.

To a solution of the appropriate Ph* ester (1.00 equiv.) in Et_2O (0.2 M) at –78 °C was added $LiAlH_4$ (1.00 equiv.) in portions. The reaction was stirred at –78 °C for 2 h and then stirred at 0 °C for an additional 10 min. After this time, the reaction was quenched by sequential dropwise addition of H_2O, aq. NaOH (15% w/v) and H_2O at 0 °C. The resulting mixture was diluted with Et_2O and $MgSO_4$ was added. The mixture was stirred vigorously for 15 min then filtered, concentrated *in vacuo* and purified by column chromatography (see experimental methods section for details).

3. Optimisation

Table S1: Optimisation of Reaction from linear precursors



Entry	[M] 4 mol%	L*	Chiral Ligand	Base (Eq)	T (°C)	Solvent	Yield[a] (%)	d.r.	e.r.[b]
1	Ir(cod)acac	**5**	(*R*)-DTBM-SEGPHOS	KO^{t}Bu (4)	110	^{t}BuOH	66	89:11	90:10
2	Ir(cod)acac	**6**	(R_P,*R*)-Taniaphos	KO^{t}Bu (2)	110	^{t}BuOH	33	93:7	50:50
3	Ir(cod)acac	**7**	Josiphos SL-J0	KO^{t}Bu (2)	110	^{t}BuOH	87	90:10	48:52
4	Ir(cod)acac	**L1**	(*R*)-DTBM-MeOBIPHEP	KO^{t}Bu (4)	110	^{t}BuOH	14	85:15	85:15
5	Ir(cod)acac	**L2**	(*R*)-DTBM-GARPHOS	KO^{t}Bu (4)	110	^{t}BuOH	18	87:13	89:11
6	Ir(cod)acac	**L3**	(*R*)-3,5-Me-4-OMe-GARPHOS	KO^{t}Bu (4)	110	^{t}BuOH	65	87:13	71:29
7	Ir(cod)acac	**L4**	(*R*)-3,5-CF_3-GARPHOS	KO^{t}Bu (4)	110	^{t}BuOH	5	85:15	63:36
8	Ir(cod)acac	**L11**	(*R*)-P-Phos	KO^{t}Bu (4)	110	^{t}BuOH	31	89:11	29:71
9	Ir(cod)acac	**L12**	(*R*)-BINAP	KO^{t}Bu (4)	110	^{t}BuOH	43	88:12	56:44
10	Ir(cod)acac	**L13**	(*R*)-Tol-BINAP	KO^{t}Bu (4)	110	^{t}BuOH	59	82:18	41:59
11	Ir(cod)acac	**L14**	(*R*)-Xyl-BINAP	KO^{t}Bu (4)	110	^{t}BuOH	41	89:11	60:40
12	Ir(cod)acac	**L15**	(*R*)-SYNPHOS	KO^{t}Bu (4)	110	^{t}BuOH	35	84:16	54:46
13	Ir(cod)acac	**L16**	(*R*)-DIFLUOROPHOS	KO^{t}Bu (4)	110	^{t}BuOH	24	86:14	73:26
14	Ir(cod)acac	**L17**	(*S*)-SDP	KO^{t}Bu (4)	110	^{t}BuOH	6	85:15	66:34
15	Ir(cod)acac	**L18**	(*S,S*)-BDPP	KO^{t}Bu (4)	110	^{t}BuOH	65	88:12	44:56
16	Ir(cod)acac	**L19**	(*R,R*)-^{i}Pr-DUPHOS	KO^{t}Bu (4)	110	^{t}BuOH	11	88:12	45:55
17	Ir(cod)acac	**L20**	(*S*)-PHANEPHOS	KO^{t}Bu (4)	110	^{t}BuOH	25	91:9	48:52
18	Ir(cod)acac	**5**	(*R*)-DTBM-SEGPHOS	KO^{t}Bu (3)	110	^{t}BuOH	82	89:11	88:12
19	Ir(cod)acac	**5**	(*R*)-DTBM-SEGPHOS	KO^{t}Bu (2)	110	^{t}BuOH	87 [84]	91:9	88:12
20	Ir(cod)acac	**5**	(*R*)-DTBM-SEGPHOS	KO^{t}Bu (1)	110	^{t}BuOH	87	92:8	83:17

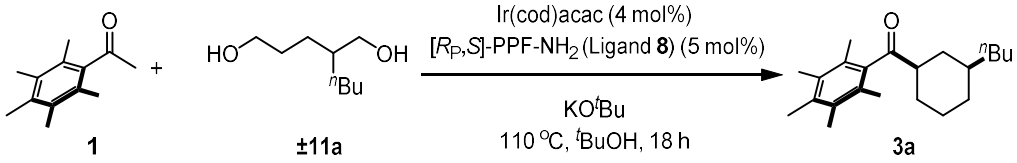
21	Ir(cod)acac	**5**	(*R*)-DTBM-SEGPHOS	KO^{t}Bu (0.5)	110	^{t}BuOH	82	93:7	78:22
22	Ir(cod)acac	**5**	(*R*)-DTBM-SEGPHOS	KO^{t}Bu (8)	110	^{t}BuOH	0	-	-
23	Ir(cod)acac	**5**	(*R*)-DTBM-SEGPHOS	LiO^{t}Bu (2)	110	^{t}BuOH	<5% (85% SM)	94:6	-
24	Ir(cod)acac	**5**	(*R*)-DTBM-SEGPHOS	KOH (2)	110	^{t}BuOH	75	92:8	83:17
25	Ir(cod)acac	**5**	(*R*)-DTBM-SEGPHOS	KOH (4)	110	^{t}BuOH	87	91:9	85:15
26	Ir(cod)acac	**5**	(*R*)-DTBM-SEGPHOS	NaOH (2)	110	^{t}BuOH	73	91:9	60:40
27	Ir(cod)acac	**5**	(*R*)-DTBM-SEGPHOS	KO^{t}Bu (2)	100	^{t}BuOH	84	93:7	89:11
28	Ir(cod)acac	**5**	(*R*)-DTBM-SEGPHOS	KO^{t}Bu (2)	90	^{t}BuOH	83	92:8	88:12
29	Ir(cod)acac	**5**	(*R*)-DTBM-SEGPHOS	KO^{t}Bu (2)	80	^{t}BuOH	80	92:8	89:11
30	Ir(cod)acac	**5**	(*R*)-DTBM-SEGPHOS	KO^{t}Bu (2)	70	^{t}BuOH	41 (37% SM)	93:7	90:10
31	Ir(cod)acac	**5**	(*R*)-DTBM-SEGPHOS	KO^{t}Bu (2)	120	^{t}BuOH	84	92:8	87:13
32	Ir(cod)acac	**5**	(*R*)-DTBM-SEGPHOS	KO^{t}Bu (2)	110	^{t}AmOH	77	93:7	85:15
33	Ir(cod)acac	**5**	(*R*)-DTBM-SEGPHOS	KO^{t}Bu (2)	110	*m*-Xylene	0 (28% SM)	-	-
34	Ir(cod)acac	**5**	(*R*)-DTBM-SEGPHOS	KO^{t}Bu (2)	110	PhMe	0 (25% SM)	-	-
35	Ir(cod)acac	**5**	(*R*)-DTBM-SEGPHOS	KO^{t}Bu (2)	110	Heptane	0 (0% SM)	-	-
36	Ir(cod)acac	**5**	(*R*)-DTBM-SEGPHOS	KO^{t}Bu (2)	110	1,4-dioxane	0 (67% SM)	-	-
37	Ir(cod)acac	**5**	(*R*)-DTBM-SEGPHOS	KO^{t}Bu (2)	110	DMF	0 (0% SM)	-	-
38	$[Ir(cod)Cl]_2$	**5**	(*R*)-DTBM-SEGPHOS	KO^{t}Bu (2)	110	^{t}BuOH	70	91:9	86:14
39	$[Ir(cod)OMe]_2$	**5**	(*R*)-DTBM-SEGPHOS	KO^{t}Bu (2)	110	^{t}BuOH	79	91:9	87:13
40	$[Ir(coe)_2Cl]_2$	**5**	(*R*)-DTBM-SEGPHOS	KO^{t}Bu (2)	110	^{t}BuOH	29	92:8	85:15
41	Ir(cod)acac	**L3**	(*R*)-3,4,5-OMe-MeOBIPHEP	KO^{t}Bu (2)	110	^{t}BuOH	82	91:9	69:31
42	Ir(cod)acac	**L21**	(*R*)-3,5-^{t}Bu-MeOBIPHEP	KO^{t}Bu (2)	110	^{t}BuOH	88	91:9	89:11
43	Ir(cod)acac	**L22**	(*R*)-amino-MeOBIPHEP	KO^{t}Bu (2)	110	^{t}BuOH	39	92:8	73:27

44	Ir(cod)acac	**L23**	(*R*)-furyl-MeOBIPHEP	KO^{t}Bu (2)	110	^{t}BuOH	70	92:8	48:52
45	Ir(cod)acac	**L24**	(*R*)-MeO-BIPHEP	KO^{t}Bu (2)	110	^{t}BuOH	87	92:8	36:64
46	Ir(cod)acac	**L25**	(*R*)-^{i}Pr-MeOBIPHEP	KO^{t}Bu (2)	110	^{t}BuOH	17	93:7	38:62
47	Ir(cod)acac	**L26**	(*R*)-MonoPhos	KO^{t}Bu (2)	110	^{t}BuOH	43	92:8	59:41
48	Ir(cod)acac	**L27**	(*R*,*R*)-DIPAMP	KO^{t}Bu (2)	110	^{t}BuOH	79	92:8	48:52
49	Ir(cod)acac	**L28**	(*R*)-C3-Tunephos	KO^{t}Bu (2)	110	^{t}BuOH	84	92:8	39:61
50	Ir(cod)acac	**L29**	Duanphos	KO^{t}Bu (2)	110	^{t}BuOH	12	92:8	55:45
51	Ir(cod)acac	**L30**	(*R*)-SEGPHOS	KO^{t}Bu (4)	110	^{t}BuOH	55	92:8	57:43
52	Ir(cod)acac	**L31**	(*R*)-Xyl-SEGPHOS	KO^{t}Bu (4)	110	^{t}BuOH	74	84:16	65:35
53	Ir(cod)acac	**8**	[R_P,*S*]-PPF-NH$_2$	KO^{t}Bu (2)	110	^{t}BuOH	82 [81]	91:9	3:97
54	Ir(cod)acac	**9**	[R_P,*S*]- **9**	KO^{t}Bu (2)	110	^{t}BuOH	14	93:7	37:63
55	Ir(cod)acac	**10**	[S_P,R]-PPF-NHMe	KO^{t}Bu (2)	110	^{t}BuOH	14	92:8	54:46
56	Ir(cod)acac	**L32**	[S_P,R]-**L32**	KO^{t}Bu (2)	110	^{t}BuOH	44	93:7	61:39
57[c]	Ir(cod)acac	**8**	[R_P,*S*]-PPF-NH$_2$	KO^{t}Bu (2)	110	^{t}BuOH	3	-	-
58[d]	Ir(cod)acac	**8**	[R_P,*S*]-PPF-NH$_2$	KO^{t}Bu (2)	110	^{t}BuOH	77	90:10	92:8
59[e]	Ir(cod)acac	**8**	[R_P,*S*]-PPF-NH$_2$	KO^{t}Bu (2)	110	^{t}BuOH	78	91:9	96:4
60	Ir(cod)acac	**8**	[R_P,*S*]-PPF-NH$_2$	KO^{t}Bu (4)	110	^{t}BuOH	59	88:12	3:97
61	Ir(cod)acac	**8**	[R_P,*S*]-PPF-NH$_2$	KO^{t}Bu (0.5)	110	^{t}BuOH	39	90:10	31:69
62	Ir(cod)acac	**8**	[R_P,*S*]-PPF-NH$_2$	NaO^{t}Bu (2)	110	^{t}BuOH	35	92:8	22:78
63	Ir(cod)acac	**8**	[R_P,*S*]-PPF-NH$_2$	KOH (2)	110	^{t}BuOH	51	92:8	33:67
64	[Ir(cod)Cl]$_2$	**8**	[R_P,*S*]-PPF-NH$_2$	KO^{t}Bu (2)	110	^{t}BuOH	64	91:9	13:87
65	[Rh(cod)Cl]$_2$	**8**	[R_P,*S*]-PPF-NH$_2$	KO^{t}Bu (2)	110	^{t}BuOH	72	92:8	44:56
66	[Ru(cod)Cl]$_n$	**8**	[R_P,*S*]-PPF-NH$_2$	KO^{t}Bu (2)	110	^{t}BuOH	41	92:8	36:64

[a]Determined by reverse phase HPLC analysis *vs* 1-bromo-2,3,4,5,6-pentamethylbenzene as an internal standard. [Isolated yields are given in parentheses]. [b] Determined by normal phase HPLC analysis using a chiral stationary

phase. [c] 10 mol% L* was used, [d] 4 mol% L* was used [e] 2 mol% Ir(cod)acac was used. The percentage of metal precatalyst refers to that of active metal species after dissociation of multimeric precursors.

Table S2: Optimisation of Reaction from diols

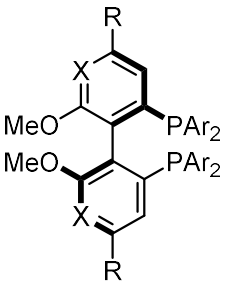


1 ±**11a** **3a**

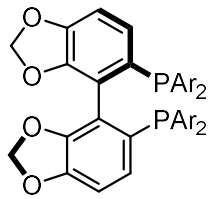
Entry	Ph*COMe eq.	Diol eq.	Conc. (M)	Base Equiv.	Yield[a] (%)	d.r.	e.r.[b]
1	1	2	0.6	2	53	91:9	70:30
2	1	2	3	2	72	92:8	72:28
3	2	1	3	2	86[83]	92:8	86:14
4	2	1	6	2	77	91:9	85:15
5	2	1	3	1	54	91:9	66:34
6	2	1	3	4	56	79:21	84:16

[a]Determined by reverse phase HPLC analysis *vs* 1-bromo-2,3,4,5,6-pentamethylbenzene as an internal standard. [b] Determined by normal phase HPLC analysis using a chiral stationary phase. [Isolated yields are given in parentheses].

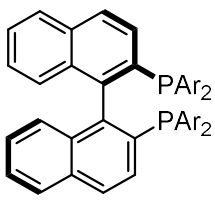
Structures of Ligands used in this Study



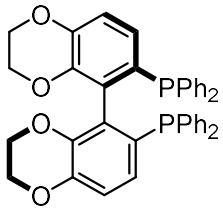
L1: X=C, R= H, Ar= DTBM
L2: X=C, R= OMe, Ar= DTBM
L3: X=C, R= OMe, Ar= 3,5-Me_2-4-(OMe)-C_6H_2
L4: X=C, R= OMe, Ar= 3,5-$(CF_3)_2$-C_6H_3
L11: X=N, R= OMe, Ar= Ph
L21: X=C, R= H, Ar = 3,5-^{t}Bu$_2$-C_6H_3
L22: X=C, R= H, Ar = 3,5-^{i}Pr$_2$-4-(NMe_2)-C_6H_2
L23: X=C, R= H, Ar = 2-furyl
L24: X=C, R= H, Ar = Ph



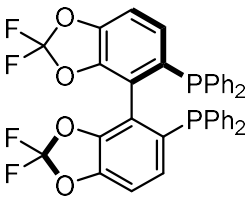
Ligand **5**: Ar = DTBM
L30: Ar = Ph
L31: Ar = Xyl



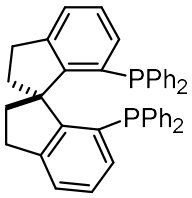
L12: Ar = Ph
L13: Ar = Tol
L14: Ar = Xyl



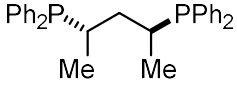
L15



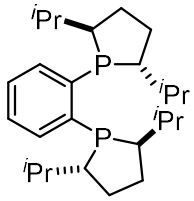
L16



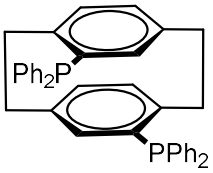
L17



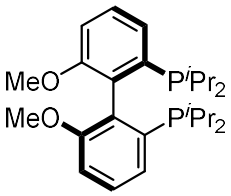
L18



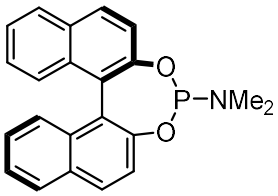
L19



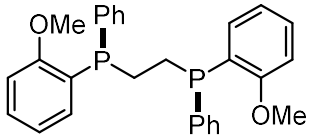
L20



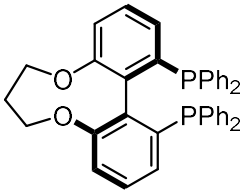
L25



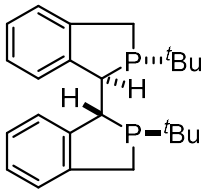
L26



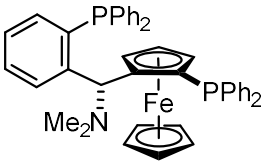
L27



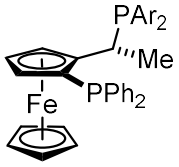
L28



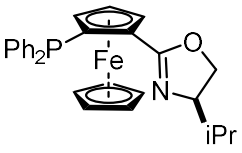
L29



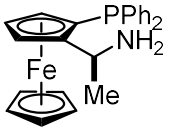
Ligand **6**



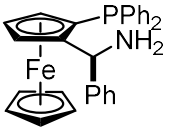
Ligand **7**
Ar = 3,5-Me_2-C_6H_3



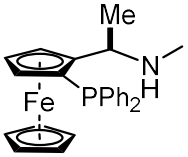
L32



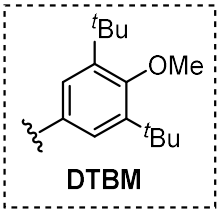
Ligand **8**



Ligand **9**



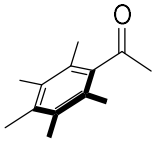
Ligand **10**



DTBM

4. Preparation and characterisation of Compounds

1-(2,3,4,5,6-Pentamethylphenyl)ethan-1-one (pentamethylacetophenone), 1



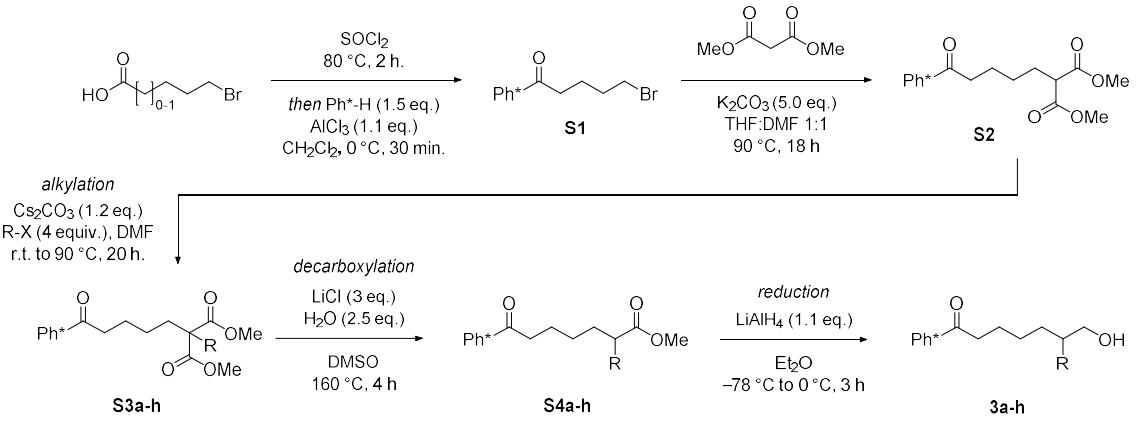
A solution of pentamethylbenzene (10.0 g, 67.4 mmol, 1.00 equiv.) and acetyl chloride (5.27 mL, 74.2 mmol, 1.10 equiv.) in CH_2Cl_2 (400 mL) was cooled to 0 °C. Aluminium chloride (11.2 g, 84.3 mmol, 1.25 equiv.) was added portionwise over 10 min. The resulting mixture was warmed to r.t. and stirred for 4 h and then poured onto crushed ice (ca. 500 g). After the ice had melted, the layers were separated and the aqueous layer was extracted CH_2Cl_2 (2 × 500 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 95:5) afforded the title compound **8** as a white solid (11.5 g, 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.46 (3H, s), 2.24 (3H, s), 2.19 (6H, s), 2.14 (6H, s).

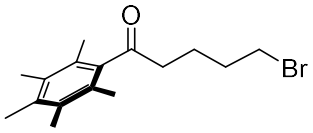
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 210.2, 141.1, 135.5, 133.2 (2 × C), 127.2 (2 × C), 33.3, 17.2, 16.8, 16.1.

The spectroscopic data was consistent with the literature. [2]

4.1 Synthesis of linear alcohol precursors



5-Bromo-1-(2,3,4,5,6-pentamethylphenyl)pentan-1-one, S1



A solution of 5-bromopentanoic acid (20.0 g, 110 mmol, 1.00 equiv.) in $SOCl_2$ (44 mL) was stirred at 80 °C for 2 h. The reaction mixture was concentrated *in vacuo* and the resulting oil was dissolved in CH_2Cl_2 (250 mL). Pentamethylbenzene (21.2 g, 143 mmol, 1.30 equiv.) was added, the reaction mixture was cooled to 0 °C and $AlCl_3$ (16.1 g, 121 mmol, 1.10 equiv.) was added portionwise over 10 min. After 1 h the mixture was poured onto ice (ca. 200 g) and conc. HCl (ca. 15 mL) and extracted with CH_2Cl_2 (2 × 250 mL). The combined organics were dried

($MgSO_4$), filtered and concentrated *in vacuo*. Purification by trituration with hexane afforded the title compound **S1** as a white solid (31.7 g, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.45 (2H, t, *J*=6.6 Hz), 2.71 (2H, t, *J*=7.1 Hz), 2.24 (3H, s), 2.19 (6H, s), 2.10 (6H, s), 2.05 – 1.92 (2H, m), 1.92 – 1.80 (2H, m).

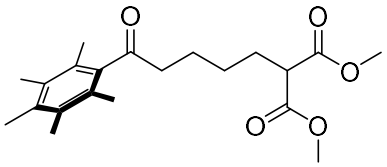
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 211.3, 140.6, 135.6, 133.3 (2 × C), 127.4 (2 × C), 44.6, 33.4, 32.2, 22.1, 17.3 (2 × C), 16.8, 16.1 (2 × C).

HRMS (ESI^+) m/z calcd. for $C_{16}H_{24}O_1Br$ $[M+H]^+$ 311.1005; found at 311.1006, Δ 0.36 ppm.

FTIR (neat) ν/cm^{-1} = 2944, 2925, 1699, 1576, 1457, 1404, 1382, 1350, 1303, 1267, 1251, 1226, 1110, 1069, 997, 918.

m.p. = 64 – 65 °C.

Dimethyl 2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate, S2



K_2CO_3 (62.1 g, 450 mmol, 5.00 equiv.) was added to a solution of dimethylmalonate (51.7 mL, 450 mmol, 5.00 equiv.) and 5-bromo-1-(2,3,4,5,6-pentamethylphenyl)pentan-1-one **S1** (27.9 g, 90.0 mmol, 1.00 equiv.) in THF/DMF (1:1, 340 mL). The mixture was stirred at 90 °C for 16 h. The reaction was cooled, diluted with H_2O (300 mL) and extracted with EtOAc (3 × 200 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo.* For ease of purification, residual dimethylmalonate was removed by distillation and the remaining crude product was purified by trituration with hexane to afford the title compound **S2** as a white solid (26.1 g, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.74 (6H, s), 3.38 (1H, t, *J*=7.5 Hz), 2.67 (2H, t, *J*=7.4 Hz), 2.23 (3H, s), 2.18 (6H, s), 2.08 (6H, s), 1.99 – 1.89 (2H, m), 1.82 – 1.70 (2H, m), 1.47 – 1.36 (2H, m).

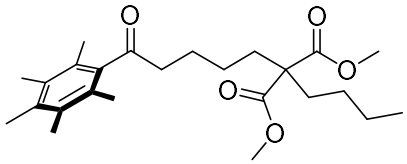
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 211.6, 169.8 (2 × C), 140.6, 135.4, 133.1 (2 × C), 127.3 (2 × C), 52.5 (2 × C), 51.5, 45.1, 28.7, 26.9, 22.9, 17.2 (2 × C), 16.7 (C), 15.9 (2 × C).

HRMS (ESI^+) m/z calcd. for $C_{21}H_{30}O_5Na$ $[M+Na]^+$ 385.1985; found at 385.1987, Δ 0.32 ppm.

FTIR (neat) ν/cm^{-1} = 2953, 2865, 1756, 1735, 1699, 1461, 1435, 1405, 1383, 1350, 1302, 1231, 1196, 1149.

m.p. = 56 – 58 °C.

Dimethyl 2-butyl-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate, S3a



Cs_2CO_3 (21.6 g, 66.2 mmol, 1.20 equiv.) was added to a solution of dimethyl 2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **S2** (20.0 g, 55.2 mmol, 1.00 equiv.) in DMF (450 mL) and stirred for 15 min at r.t. Butyl iodide (25.0 mL, 221 mmol, 4.00 equiv.) was added and the resulting mixture was stirred for 21 h. The reaction mixture was quenched with sat. aq. NH_4Cl (300 mL) and extracted with Et_2O (3 × 350 mL). The combined organic extracts were washed with LiCl (5 wt%, 3 × 200 mL), brine (3 × 300 mL), dried ($MgSO_4$) and concentrated *in vacuo.* Purification by trituration with hexane afforded the title compound **S3a** as a white solid (21.4 g, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.71 (6H, s), 2.66 (2H, t, *J*=7.5 Hz), 2.23 (3H, s), 2.18 (6H, s), 2.08 (6H, s), 1.96 – 1.82 (4H, m, C4-H_2), 1.72 (2H, qn, *J*=7.5 Hz), 1.39 – 1.18 (4H, m), 1.18 – 1.05 (2H, m), 0.89 (3H, t, *J*=7.3 Hz).

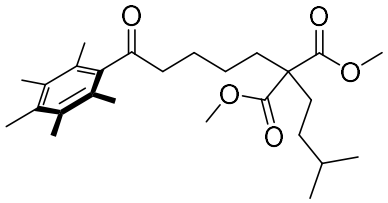
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 211.8, 172.5 (2 × C), 140.8, 135.5, 133.2 (2 × C), 127.4 (2 × C), 57.7, 52.4 (2 × C), 45.4, 32.5, 32.5, 26.4, 23.9, 23.7, 23.0, 17.4 (2 × C), 16.8, 16.1 (2 × C), 14.0.

HRMS (ESI^+) m/z calcd. for $C_{25}H_{39}O_5$ $[M+H]^+$ 419.2792; found at 419.2792, Δ 0.06 ppm.

FTIR (neat) ν/cm^{-1} = 2955, 1733, 1700, 1461, 1433, 1405, 1381, 1304, 1266, 1203, 1157, 1128, 1077.

m.p. = 92 – 93 °C.

Dimethyl 2-isopentyl-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate, S3b



1-Bromo-3-methylbutane (5.27 mL, 44.0 mmol, 4.00 equiv.), dimethyl 2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **S2** (4.00 g, 11.0 mmol, 1.00 equiv.), Cs_2CO_3 (4.30 g, 13.2 mmol, 1.20 equiv.) and DMF (90 mL) were subjected to **General Procedure C** and stirred at r.t. for 24 h and then at 80 °C for a further 8 h. Purification by column chromatography (Pentane:Et_2O, 85:15) afforded the title compound **3b** as a white solid (2.30 g, 48%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.71 (6H, s), 2.66 (2H, t, *J*=7.4 Hz), 2.23 (3H, s), 2.18 (6H, s), 2.08 (6H, s), 2.01 – 1.83 (4H, m), 1.72 (2H, p, *J*=7.5 Hz), 1.51 (1H, dp, *J*=13.2, 6.7 Hz), 1.32 – 1.14 (2H, m), 1.11 – 0.95 (2H, m), 0.88 (6H, d, *J*=6.6 Hz).

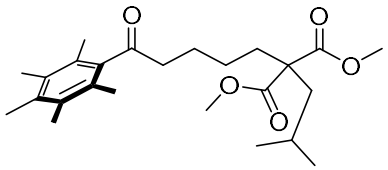
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 211.8, 172.5 (2 × C), 140.8, 135.5, 133.2 (2 × C), 127.4 (2 × C), 57.7, 52.4 (2 × C), 45.4, 33.1, 32.4, 30.5, 28.4, 23.9, 23.7, 22.6 (2 × C), 17.4 (2 × C), 16.8, 16.1 (2 × C).

HRMS (ESI^+) m/z calcd. for $C_{26}H_{41}O_5$ $[M+H]^+$ 433.2949; found at 433.2952, Δ 0.80 ppm.

FTIR (neat) ν/cm^{-1} = 2955, 1735, 1701, 1459, 1265, 1206, 1168, 1133, 1082, 1012, 918, 735.

m.p. = 82 – 83 °C.

Dimethyl 2-isobutyl-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate, S3c



1-Bromo-2-methylpropane (3.61 mL, 33.2 mmol, 4.00 equiv.), dimethyl 2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **S2** (3.00 g, 8.3 mmol, 1.00 equiv.), Cs_2CO_3 (3.26 g, 10.0 mmol, 1.20 equiv.) and DMF (70 mL) were subjected to **General Procedure C** and stirred at r.t. for 48 h. Purification by column chromatography (Pentane:Et_2O, 85:15 to 80:20) afforded the title compound **S3c** as a pale yellow solid (2.09 g, 60%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.70 (6H, s), 2.66 (2H, t, *J*=7.5 Hz), 2.23 (3H, s), 2.18 (6H, s), 2.08 (6H, s), 1.99 – 1.89 (2H, m), 1.88 (2H, d, *J*=6.4 Hz), 1.72 (2H, p, *J*=7.6 Hz), 1.66 – 1.51 (1H, m), 1.27 – 1.17 (2H, m), 0.86 (6H, d, *J*=6.7 Hz).

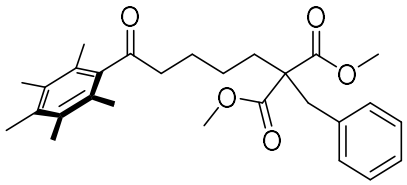
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 211.8, 172.7 (2 × C), 140.8, 135.5, 133.2 (2 × C), 127.4 (2 × C), 57.0, 52.4 (2 × C), 45.4, 41.0, 32.7, 24.2, 24.0, 23.7 (2 × C), 23.7, 17.4 (2 × C), 16.8, 16.1 (2 × C).

HRMS (ESI$^+$) m/z calcd. for $C_{25}H_{39}O_5$ $[M+H]^+$ 419.2792; found at 419.2796, Δ 0.94 ppm.

FTIR (neat) v/cm^{-1} = 2954, 1733, 1700, 1435, 1238, 1163, 1129, 1077, 1011, 911, 732, 648.

m.p. = 69 – 70 °C.

Dimethyl 2-benzyl-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate, S3d



Benzyl bromide (5.23 mL, 44.0 mmol, 4.00 equiv.), dimethyl 2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **S2** (4.00 g, 11.0 mmol, 1.00 equiv.), Cs_2CO_3 (4.30 g, 13.2 mmol, 1.20 equiv.) and DMF (90 mL) were subjected to **General Procedure C** and stirred at r.t. for 24 h and then at 80 °C for a further 8 h. Purification by column chromatography (Pentane:Et_2O, 85:15) afforded the title compound **S3d** as a white solid (2.07 g, 42%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.32 – 7.20 (3H, m), 7.10 – 7.03 (2H, m), 3.71 (6H, d, *J*=1.5 Hz), 3.24 (2H, s), 2.67 (2H, t, *J*=7.4 Hz), 2.23 (3H, s), 2.18 (6H, s), 2.08 (6H, s), 1.88 – 1.78 (2H, m), 1.72 (2H, p, *J*=7.5 Hz), 1.37 (2H, dtd, *J*=12.3, 8.6, 6.5 Hz).

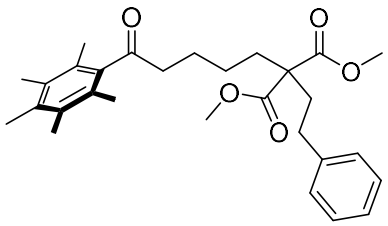
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 211.8, 171.8 (2 × C), 140.7, 136.1, 135.5, 133.2 (2 × C), 129.9 (2 × C), 128.5 (2 × C), 127.4 (2 × C), 127.2, 59.0, 52.5 (2 × C), 45.3, 38.6, 32.1, 24.0, 23.6, 17.3 (2 × C), 16.8, 16.1 (2 × C).

HRMS (ESI$^+$) m/z calcd. for $C_{28}H_{36}O_5Na$ $[M+Na]^+$ 475.2455; found at 475.2460, Δ 1.05 ppm.

FTIR (neat) v/cm^{-1} = 2951, 1736, 1699, 1496, 1455, 1266, 1198, 1178, 1125, 1086, 1031, 915, 735.

m.p. = 92 – 93 °C.

Dimethyl 2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)-2-phenethylmalonate, S3e



(2-bromoethyl)Benzene (4.52 mL, 33.2 mmol, 4.00 equiv.), dimethyl 2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **S2** (3.00 g, 8.3 mmol, 1.00 equiv.), Cs_2CO_3 (3.26 g, 10.0 mmol, 1.20 equiv.) and DMF (70 mL) were subjected to **General Procedure C** and stirred at r.t. for 48 h. Purification by column chromatography (Pentane:Et_2O, 85:15 to 80:20) afforded the title compound **S3e** an oil which solidified on standing to a white solid (2.73 g, 71%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.31 – 7.24 (2H, m), 7.23 – 7.14 (3H, m), 3.72 (6H, s), 2.67 (2H, t, *J*=7.4 Hz), 2.55 – 2.46 (2H, m), 2.23 (3H, s), 2.22 – 2.19 (2H, m), 2.18 (6H, s), 2.09 (6H, s), 2.04 – 1.97 (2H, m), 1.73 (2H, p, *J*=7.6 Hz), 1.34 – 1.24 (2H, m).

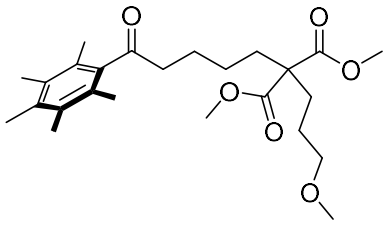
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 211.8, 172.1 (2 × C), 141.4, 140.7, 135.5, 133.2 (2 × C), 128.6 (2 × C), 128.5 (2 × C), 127.4 (2 × C), 126.2, 57.7, 52.6 (2 × C), 45.4, 34.7, 32.9, 30.8, 23.9, 23.6, 17.4 (2 × C), 16.8, 16.1 (2 × C).

HRMS (ESI$^+$) m/z calcd. for $C_{29}H_{39}O_5$ $[M+H]^+$ 467.2792; found at 467.2794, Δ 0.42 ppm.

FTIR (neat) ν/cm^{-1} = 2951, 2360, 1732, 1699, 1454, 1247, 1175, 1124, 910, 732, 700, 649.

m.p. = 141 – 142 °C.

Dimethyl 2-(3-methoxypropyl)-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate, S3f



1-Bromo-3-methoxypropane (4.95 mL, 44.0 mmol, 4.00 equiv.), dimethyl 2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **S2** (4.00 g, 11.0 mmol, 1.00 equiv.), Cs_2CO_3 (4.30 g, 13.2 mmol, 1.20 equiv.) and DMF (90 mL) were subjected to **General Procedure C** and stirred at r.t. for 24 h. Purification by column chromatography (Pentane:Et_2O, 85:15 to 80:20) afforded the title compound **S3f** as a white solid (2.65 g, 55%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.71 (6H, s), 3.36 (2H, t, *J*=6.4 Hz), 3.31 (3H, s), 2.66 (2H, t, *J*=7.4 Hz), 2.23 (3H, s), 2.18 (6H, s), 2.08 (6H, s), 1.98 – 1.85 (4H, m), 1.71 (2H, p, *J*=7.6 Hz), 1.52 – 1.39 (2H, m), 1.32 – 1.18 (2H, m).

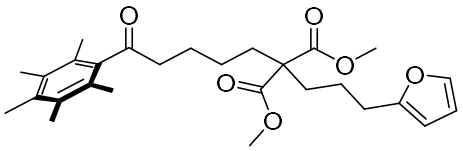
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 211.8, 172.2 (2 × C), 140.8, 135.5, 133.2 (2 × C), 127.4 (2 × C), 72.6, 58.7, 57.5, 52.5 (2 × C), 45.4, 32.8, 29.6, 24.6, 23.9, 23.6, 17.4 (2 × C), 16.8, 16.1 (2 × C).

HRMS (ESI$^+$) m/z calcd. for $C_{25}H_{39}O_6$ $[M+H]^+$ 435.2741; found at 435.2750, Δ 2.02 ppm.

FTIR (neat) ν/cm^{-1} = 2952, 2360, 1734, 1700, 1456, 1387, 1210, 1120, 1002, 918, 865, 735, 647.

m.p. = 81 – 82 °C.

Dimethyl-2-(3-(furan-2-yl)propyl)-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate, S3g



2-(2-bromoethyl)Furan (3.93 g, 20.8 mmol, 4.00 equiv.), dimethyl 2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **S2** (1.90 g, 5.20 mmol, 1.00 equiv.), Cs_2CO_3 (3.05 g, 9.3 mmol, 1.80 equiv.) and DMF (50 mL) were subjected to **General Procedure C** and stirred at r.t. for 21 h. Purification by column chromatography (Pentane:Et_2O, 95:5 to 80:20) afforded the title compound **S3g** as a white solid (1.74 g, 71%).

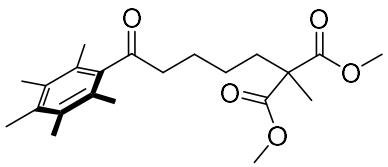
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.28 (1H, dd, J = 2.0, 0.8 Hz), 6.26 (1H, dd, J = 3.2, 2.0 Hz), 5.99 (1H, dd, J = 3.2, 0.8 Hz), 3.71 (6H, s), 2.68 – 2.60 (4H, m), 2.23 (3H, s), 2.18 (6H, s), 2.09 (6H, s), 1.96 – 1.87 (4H, m), 1.71 (2H p, J = 7.5 Hz), 1.58 – 1.45 (2H, m), 1.28 – 1.12 (2H, m).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 211.7, 172.2 (2 × C), 155.4, 141.0, 140.8, 135.5, 133.2 (2 × C), 127.4 (2 × C), 110.2, 105.3, 57.6, 52.5 (2 × C), 45.4, 32.6, 32.1, 28.1, 23.8, 23.6, 22.8, 17.4 (2 × C), 16.8, 16.1 (2 × C).

HRMS (ESI^+) m/z calcd. for $C_{28}H_{38}O_6Na$ $[M+Na]^+$ 493.2561; found at 493.2583, Δ 4.53 ppm.

FTIR (neat) ν/cm^{-1} = 2953, 1733, 1700, 1670, 1507, 1458, 1216, 1167, 1091, 1003.

Dimethyl 2-methyl-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate, S3h



Methyl iodide (2.07 mL, 33.2 mmol, 4.00 equiv.), dimethyl 2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **S2** (3.00 g, 8.3 mmol, 1.00 equiv.), Cs_2CO_3 (3.26 g, 10.0 mmol, 1.20 equiv.) and DMF (70 mL) were subjected to **General Procedure C** and stirred at r.t. for 24 h. Purification by column chromatography (Pentane:Et_2O, 85:15) afforded the title compound **S3h** as a white solid (1.40 g, 45%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.71 (6H, s), 2.67 (2H, t, *J*=7.4 Hz), 2.23 (3H, s), 2.18 (6H, s), 2.08 (6H, s), 1.93 – 1.84 (2H, m), 1.72 (2H, p, *J*=7.6 Hz), 1.41 (3H, s), 1.35 – 1.23 (3H, m).

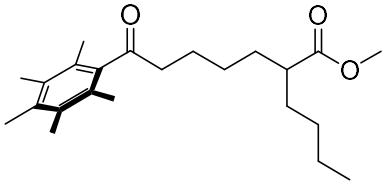
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 211.9, 172.9 (2 × C), 140.8, 135.5, 133.2 (2 × C), 127.4 (2 × C), 53.8, 52.6 (2 × C), 45.4, 35.7, 24.1, 23.6, 20.2, 17.4 (2 × C), 16.8, 16.1 (2 × C).

HRMS (ESI^+) m/z calcd. for $C_{22}H_{32}O_5Na$ $[M+Na]^+$ 399.2142; found at 399.2147, Δ 1.25 ppm.

FTIR (neat) ν/cm^{-1} = 2953, 1735, 1700, 1463, 1380, 1254, 1164, 1115, 987, 913, 873, 733.

m.p. = 81 – 82 °C.

Methyl 2-butyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate, S4a



Dimethyl 2-butyl-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **S3a** (20.4 g, 48.8 mmol, 1.00 equiv.) was added to a solution of LiCl (6.21 mg, 146 mmol, 3.00 equiv.) in H_2O (2.20 mL) and DMSO (90 mL) and the resulting reaction mixture was stirred at 140 °C for 3 h. The reaction mixture was cooled and extracted with Et_2O (3 × 150 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo.* Purification by column chromatography (Pentane:Et_2O 90:10) afforded the title compound **S4a** as a white solid (15.4 g, 87%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.67 (3H, s), 2.65 (2H, t, *J*=7.5 Hz), 2.35 (1H, tt, *J*=8.9, 5.3 Hz), 2.23 (3H, s), 2.18 (6H, s), 2.08 (6H, s), 1.80 – 1.55 (4H, m), 1.55 – 1.40 (2H, m), 1.40 – 1.17 (6H, m), 0.88 (3H, t, *J*=7.1 Hz).

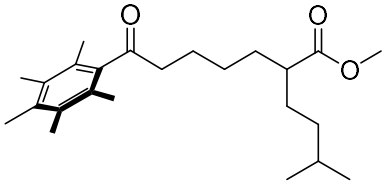
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.0, 177.0, 140.9, 135.5, 133.2 (2 × C), 127.4 (2 × C), 51.5, 45.7, 45.5, 32.4 (2 × C), 29.8, 27.2, 23.3, 22.7, 17.3 (2 × C), 16.8, 16.1 (2 × C), 14.1.

HRMS (ESI$^+$) m/z calcd. for $C_{23}H_{37}O_3$ $[M+H]^+$ 361.2737; found at 361.2737, Δ 0.04 ppm.

FTIR (neat) v/cm^{-1} = 3018, 2935, 2860, 2012, 1736, 1701, 1456, 1379, 1303, 1264, 1193, 1168, 1113, 1000, 916.

m.p. = 96 – 97 °C.

Methyl 2-isopentyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate, S4b



Dimethyl 2-isopentyl-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **S3b** (2.26 g, 5.22 mmol, 1.00 equiv.), LiCl (664 mg, 15.7 mmol, 3.00 equiv.), H_2O (0.23 mL) and DMSO (10 mL) were subjected to **General Procedure D** and stirred at 160 °C for 4 h. The reaction mixture was cooled and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 95:5 to 93:7) afforded the title compound **S4b** as a clear oil (1.26 g, 64%).

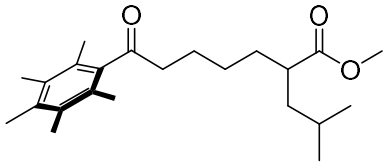
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.67 (3H, s), 2.66 (2H, t, *J*=7.5 Hz), 2.32 (1H, tt, *J*=8.9, 5.3 Hz), 2.23 (3H, s), 2.18 (6H, s), 2.08 (6H, s), 1.79 – 1.55 (4H, m), 1.55 – 1.40 (3H, m), 1.40 – 1.28 (2H, m), 1.21 – 1.06 (2H, m), 0.87 (3H, d, *J*=6.6 Hz), 0.86 (3H, d, *J*=6.6 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.0, 177.0, 140.9, 135.5, 133.2 (2 × C), 127.4 (2 × C), 51.5, 45.9, 45.5, 36.7, 32.4, 30.5, 28.1, 27.2, 23.3, 22.7, 22.6, 17.3 (2 × C), 16.8, 16.1 (2 × C).

HRMS (ESI$^+$) m/z calcd. for $C_{24}H_{39}O_3$ $[M+H]^+$ 375.2894; found at 375.2902, Δ= 2.20 ppm.

FTIR (neat) v/cm^{-1} = 2952, 2869, 1737, 1702, 1459, 1405, 1384, 1366, 1303, 1258, 1193, 1169, 1069, 1001, 918, 852, 739, 634.

Methyl 2-methyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate, S4c



Dimethyl 2-isobutyl-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **S3c** (1.80 g, 4.30 mmol, 1.00 equiv.), LiCl (547 mg, 12.9 mmol, 3.00 equiv.), H_2O (0.19 mL) and DMSO (10 mL) were subjected to **General Procedure D** and stirred at 160 °C for 4 h. The reaction mixture was cooled and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 95:5 to 93:7) afforded the title compound **S4c** as a clear oil (1.22 g, 68%).

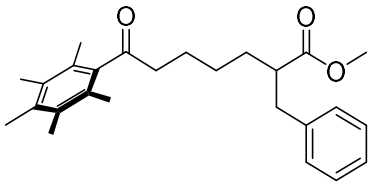
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.66 (3H, s), 2.65 (2H, t, *J*=7.4 Hz), 2.45 (1H, tt, *J*=9.3, 5.2 Hz), 2.23 (3H, s), 2.18 (6H, s), 2.08 (6H, s), 1.81 – 1.42 (6H, m), 1.42 – 1.27 (2H, m), 1.23 (1H, ddd, *J*=13.1, 8.0, 5.3 Hz), 0.89 (3H, d, *J*=6.5 Hz), 0.87 (3H, d, *J*=6.5 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.0, 177.2, 140.9, 135.5, 133.2 (2 × C), 127.4 (2 × C), 51.5, 45.5, 43.7, 41.9, 32.9, 27.2, 26.4, 23.3, 23.1, 22.3, 17.3 (2 × C), 16.8, 16.1 (2 × C).

HRMS (ESI^+) m/z calcd. For $C_{23}H_{37}O_3$ $[M+H]^+$ 361.2737; found at 361.2747, Δ= 2.70 ppm.

FTIR (neat) v/cm^{-1} = 2950, 2869, 1736, 1701, 1461, 1405, 1383, 1265, 1194, 1167, 1123, 1069, 1000, 920, 732.

Methyl 2-benzyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate, S4d



Dimethyl 2-benzyl-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **S3d** (2.02 g, 4.46 mmol, 1.00 equiv.), LiCl (567 mg, 13.4 mmol, 3.00 equiv.), H_2O (0.20 mL) and DMSO (10 mL) were subjected to **General Procedure D** and stirred at 160 °C for 2 h. The reaction mixture was cooled and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 95:5 to 93:7) afforded the title compound **S4d** as a clear oil (936 mg, 53%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.29 – 7.23 (2H, m), 7.23 – 7.17 (1H, m), 7.16 – 7.12 (2H, m), 3.60 (3H, s), 2.94 (1H, dd, *J*=13.4, 8.0 Hz), 2.74 (1H, dd, *J*=13.4, 6.7 Hz), 2.71 – 2.65 (1H, m), 2.63 (2H, t, *J*=7.2 Hz), 2.22 (3H, s), 2.17 (6H, s), 2.07 (6H, s), 1.80 – 1.61 (3H, m), 1.57 – 1.47 (1H, m), 1.42 – 1.31 (2H, m).

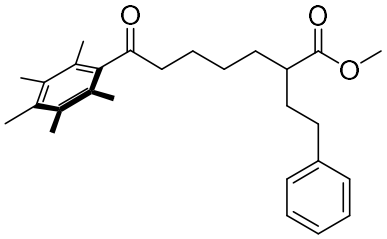
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.0 , 176.2, 140.8, 139.4, 135.5, 133.2 (2 × C), 129.0 (2 × C), 128.5 (2 × C), 127.4 (2 × C), 126.5, 51.6, 47.6, 45.4, 38.7, 32.0, 27.1, 23.2, 17.3 (2 × C), 16.8, 16.1 (2 × C).

HRMS (ESI^+) m/z calcd. for $C_{26}H_{35}O_3$ $[M+H]^+$ 395.2581; found at 395.2587, Δ 1.58 ppm.

FTIR (neat) v/cm^{-1} = 2947, 2360, 1736, 1700, 1496, 1455, 1380, 1201, 1163, 1119, 1071, 744, 701.

m.p. = 93 – 94 °C.

Methyl 7-oxo-7-(2,3,4,5,6-pentamethylphenyl)-2-phenethylheptanoate, S4e



Dimethyl 2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)-2-phenethylmalonate **S3e** (2.71 g, 5.80 mmol, 1.00 equiv.), LiCl (738 mg, 17.4 mmol, 3.00 equiv.), H_2O (0.26 mL) and DMSO (10 mL) were subjected to **General Procedure D** and stirred at 160 °C for 4 h. The reaction mixture was cooled and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 95:5 to 93:7) afforded the title compound **S4e** as a pale yellow oil (1.14 g, 48%).

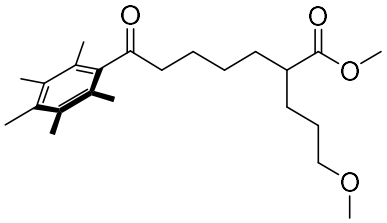
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.31 – 7.24 (2H, m), 7.21 – 7.14 (3H, m), 3.68 (3H, s), 2.65 (2H, t, *J*=7.4 Hz), 2.63 – 2.53 (2H, m), 2.42 (1H, tt, *J*=8.9, 5.2 Hz), 2.23 (3H, s), 2.18 (6H, s), 2.08 (6H, s), 1.97 (1H, dtd, *J*=13.5, 9.3, 5.9 Hz), 1.82 – 1.63 (4H, m), 1.53 (1H, ddt, *J*=13.5, 10.9, 5.7 Hz), 1.40 – 1.28 (2H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 211.9, 176.6, 141.7, 140.8, 135.5, 133.2 (2 × C), 128.5 (2 × C), 128.5 (2 × C), 127.4 (2 × C), 126.1, 51.6, 45.5, 45.1, 34.2, 33.8, 32.4, 27.1, 23.3, 17.3 (2 × C), 16.8, 16.1 (2 × C).

HRMS (ESI^+) m/z calcd. for $C_{27}H_{37}O_3$ $[M+H]^+$ 409.2737; found at 409.2745, Δ 1.89 ppm.

FTIR (neat) ν/cm^{-1} = 2945, 2360, 1734, 1699, 1496, 1454, 1381, 1303, 1262, 1200, 1158, 1120, 1070, 1029, 912, 741, 700.

Methyl 2-(3-methoxypropyl)-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate, S4f



Dimethyl 2-(3-methoxypropyl)-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **S3f** (2.65 g, 6.10 mmol, 1.00 equiv.), LiCl (776 mg, 18.0 mmol, 3.00 equiv.), H_2O (0.27 mL) and DMSO (12 mL) were subjected to **General Procedure D** and stirred at 160 °C for 2 h. The reaction mixture was cooled and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 90:10) afforded the title compound **S4f** as a clear oil (1.42 g, 62%).

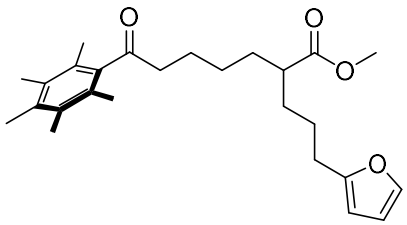
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.67 (3H, s), 3.35 (2H, td, *J*=5.6, 2.6 Hz), 3.32 (3H, s), 2.65 (2H, t, *J*=7.4 Hz), 2.38 (1H, tt, *J*=9.1, 4.6 Hz), 2.23 (3H, s), 2.18 (6H, s), 2.08 (6H, s), 1.79 – 1.61 (4H, m), 1.59 – 1.45 (4H, m), 1.35 (2H, tq, *J*=9.6, 6.0 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.0, 176.7, 140.8, 135.5, 133.2 (2 × C), 127.4 (2 × C), 72.5, 58.7, 51.6, 45.5, 45.4, 32.4, 29.1, 27.6, 27.1, 23.3, 17.3 (2 × C), 16.8, 16.1 (2 × C).

HRMS (ESI^+) m/z calcd. for $C_{23}H_{37}O_4$ $[M+H]^+$ 377.2686; found at 377.2698, Δ 3.07 ppm.

FTIR (neat) ν/cm^{-1} = 2989, 2865, 1736, 1701, 1454, 1383, 1197, 1165, 1121, 1001, 916, 842.

Dimethyl-2-(3-(furan-2-yl)propyl)-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate, S4g



Dimethyl-2-(3-(furan-2-yl)propyl)-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **S3g** (1.20 g, 2.55 mmol, 1.00 equiv.), LiCl (324 mg, 7.65 mmol, 3.00 equiv.), H_2O (0.12 mL) and DMSO (6 mL) were subjected to **General Procedure D** and stirred at 160 °C for 2.5 h. The reaction mixture was cooled and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Pentane:EtOAc, 99:1 → 95:5) afforded the title compound **S4g** as a colourless oil (610 mg, 58%).

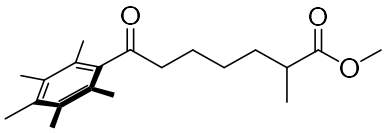
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.32 – 7.25 (1H, m), 6.27 (1H, dd, *J* = 3.2, 1.9 Hz), 5.98 (dd, *J* = 3.2, 1.9 Hz,), 3.67 (3H, s, C7-H_3), 2.81 – 2.52 (4H, m), 2.45 – 2.32 (1H, m), 2.23 (3H, s), 2.18 (6H, s), 2.09 (6H, s), 1.80 – 1.57 (6H, m), 1.56 – 1.45 (2H, m), 1.42 – 1.29 (2H, m).

^{13}C NMR (101 MHz, $CDCl_3$) δ 211.9, 176.7, 155.9, 140.9, 140.8, 135.5, 133.2 (2 × C), 127.4 (2 × C), 110.2, 104.9, 51.6, 45.5, 45.4, 32.4, 31.9, 27.9, 27.1, 26.0, 23.3, 17.3 (2 × C), 16.8, 16.1 (2 × C).

HRMS (ESI$^+$) m/z calcd. for $C_{26}H_{36}O_4Na$ $[M+Na]^+$ 335.2506; found at 335.2503, Δ 0.66 ppm.

FTIR (neat) ν/cm^{-1} = 2947, 2360, 2341, 1735, 1700, 1507, 1457, 1153, 1005, 923, 732, 668, 650.

Methyl 2-methyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate, S4h



Dimethyl 2-methyl-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **S3h** (1.38 g, 3.67 mmol, 1.00 equiv.), LiCl (467 mg, 11.0 mmol, 3.00 equiv.), H_2O (0.17 mL) and DMSO (10 mL) were subjected to **General Procedure D** and stirred at 160 °C for 4 h. The reaction mixture was cooled and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 95:5 to 93:7) afforded the title compound **S4h** as a white solid (732 mg, 63%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.67 (3H, s), 2.73 – 2.60 (2H, m), 2.54 – 2.41 (1H, m), 2.23 (3H, s), 2.18 (6H, s), 2.09 (6H, s), 1.77 – 1.64 (3H, m), 1.53 – 1.31 (3H, m), 1.15 (3H, d, *J*=7.0 Hz).

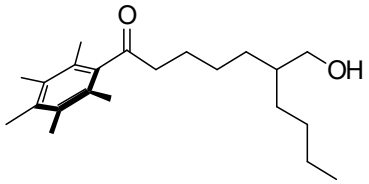
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 212.0, 177.3, 140.9, 135.5, 133.2 (2 × C), 127.4 (2 × C), 51.6, 45.5, 39.5, 33.7, 26.9, 23.3, 17.3 (2 × C), 17.2, 16.8, 16.1 (2 × C).

HRMS (ESI$^+$) m/z calcd. for $C_{20}H_{30}NaO_3$ $[M+Na]^+$ 341.2087; found at 341.2088, Δ 0.38 ppm.

FTIR (neat) ν/cm^{-1} = 3654, 2980, 2938, 1736, 1699, 1461, 1381, 1303, 1260, 1196, 1159, 1131, 1075, 991, 839.

m.p. = 52 – 54 °C.

6-(Hydroxymethyl)-1-(2,3,4,5,6-pentamethylphenyl)decan-1-one, 3a



$LiAlH_4$ (994 mg, 26.2 mmol, 1.00 equiv.), methyl 2-butyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate **S4a** (9.43 g, 26.2 mmol, 1.00 equiv.) and Et_2O (130 mL) were subjected to **General Procedure E**. The reaction was quenched by sequential dropwise addition of H_2O (0.99 mL), aq. NaOH (15% w/v, 0.99 mL) and H_2O (2.97 mL) at 0 °C. Purification by column chromatography (Pentane:Et_2O, 80:20 to 60:40) afforded title compound **3a** as an oil which solidified on standing to a white solid (6.73 g, 77%, **3a**).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.55 (2H, d, *J*=5.5 Hz), 2.72 – 2.64 (2H, m), 2.23 (3H, s), 2.18 (6H, s), 2.09 (6H, s), 1.76 – 1.67 (2H, m), 1.48 (1H, p, *J*=5.8 Hz), 1.44 – 1.21 (10H, m), 0.93 – 0.86 (3H, m).

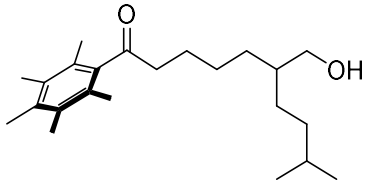
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.2, 140.9, 135.5, 133.2 (2 × C), 127.4 (2 × C), 65.7, 45.7, 40.5, 30.9, 30.8, 29.3, 26.6, 23.7, 23.2, 17.3 (2 × C), 16.8, 16.1 (2 × C), 14.2.

HRMS (ESI^+) m/z calcd. for $C_{22}H_{37}O_2$ $[M+H]^+$ 333.2788; found at 333.2788, Δ 0.09 ppm.

FTIR (neat) v/cm^{-1} = 3447, 2955, 2928, 2856, 1576, 1464, 1403, 1381, 1359, 1303, 1263, 1127, 1069, 1041, 996, 934, 919, 795, 729.

m.p. = 46 – 48 °C.

6-(hydroxymethyl)-9-Methyl-1-(2,3,4,5,6-pentamethylphenyl)decan-1-one, 3b



$LiAlH_4$ (91.5 mg, 2.41 mmol, 1.00 equiv.), methyl 2-isopentyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate **S4b** (904 mg, 2.41 mmol, 1.00 equiv.) and Et_2O (15 mL) were subjected to **General Procedure E**. The reaction was quenched by sequential dropwise addition of H_2O (0.09 mL), aq. NaOH (15% w/v, 0.09 mL) and H_2O (0.27 mL) at 0 °C. Purification by column chromatography (Pentane:Et_2O, 75:25 to 70:30) afforded the title compound **3b** as a clear oil (669 mg, 80%).

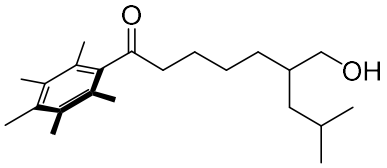
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.54 (2H, d, *J*=5.4 Hz), 2.68 (2H, t, *J*=7.4 Hz), 2.23 (3H, s), 2.18 (6H, s), 2.09 (6H, s), 1.72 (2H, p, *J*=7.4 Hz), 1.55 – 1.21 (8H, m), 1.21 – 1.12 (2H, m), 0.88 (6H, d, *J*=6.6 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.3, 140.9, 135.5, 133.2 (2 × C), 127.4 (2 × C), 65.7, 45.7, 40.8, 36.2, 30.9, 28.8, 28.5, 26.6, 23.7, 22.8, 22.7, 17.3 (2 × C), 16.8, 16.1 (2 × C).

HRMS (ESI^+) m/z calcd. for $C_{23}H_{38}O_2$ $[M+H]^+$ 347.2945; found at 347.2955, Δ 2.99 ppm.

FTIR (neat) v/cm^{-1} = 3431, 2928, 2868, 1696, 1466, 1403, 1384, 1365, 1043, 913, 736, 647, 632.

6-(hydroxymethyl)-8-Methyl-1-(2,3,4,5,6-pentamethylphenyl)nonan-1-one, 3c



$LiAlH_4$ (71 mg, 1.86 mmol, 1.00 equiv.), methyl 2-methyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate **S4c** (670 mg, 1.86 mmol, 1.00 equiv.) and Et_2O (15 mL) were subjected to **General Procedure E**. The reaction was quenched by sequential dropwise addition of H_2O (0.07 mL), aq. NaOH (15% w/v, 0.07 mL) and H_2O (0.21 mL) at 0 °C. Purification by column chromatography (Pentane:Et_2O, 70:30 to 65:35) afforded the title compound **3c** as a white solid (453 mg, 73%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.55 (1H, dd, *J*=10.7, 5.1 Hz), 3.51 (1H, dd, *J*=10.7, 5.6 Hz), 2.69 (2H, t, *J*=7.4 Hz), 2.23 (3H, s), 2.18 (6H, s), 2.09 (6H, s), 1.77 – 1.68 (2H, m), 1.68 – 1.60 (1H, m), 1.55 (1H, hept, *J*=5.4 Hz), 1.44 – 1.35 (3H, m), 1.34 – 1.27 (1H, m), 1.19 (1H, dt, *J*=13.9, 7.0 Hz), 1.09 (1H, dt, *J*=13.9, 7.1 Hz), 0.89 (3H, d, *J*=6.6 Hz), 0.88 (3H, d, *J*=6.6 Hz).

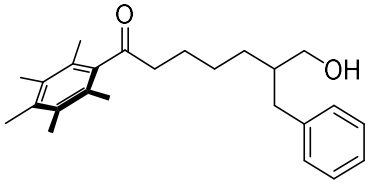
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.3, 140.9, 135.4, 133.2 (2 × C), 127.4 (2 × C), 65.9, 45.7, 40.8, 38.1, 31.2, 26.5, 25.5, 23.7, 23.1, 23.0, 17.3 (2 × C), 16.8, 16.1 (2 × C).

HRMS (ESI^+) m/z calcd. for $C_{22}H_{37}O_2$ $[M+H]^+$ 333.2788; found at 333.2800, Δ 3.57 ppm.

FTIR (neat) ν/cm^{-1} = 3432, 2952, 1700, 1466, 1384, 1043, 918, 735.

m.p. = 39 °C.

6-Benzyl-7-hydroxy-1-(2,3,4,5,6-pentamethylphenyl)heptan-1-one, 3d



$LiAlH_4$ (89.2 mg, 2.35 mmol, 1.00 equiv.) was added portionwise to a solution of methyl 2-isopentyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate **S4d** (928 mg, 2.35 mmol, 1.00 equiv.) in Et_2O:THF (3:1, 20 mL) at –78 °C. The reaction was stirred at –78 °C for 2 h and then due to insolubility, the reaction was warmed to –17 °C for 20 min. After this time, the reaction was quenched by sequential dropwise addition of H_2O (0.09 mL), aq. NaOH (15% w/v, 0.09 mL) and H_2O (0.27) at –17 °C. The reaction mixture was diluted with Et_2O and $MgSO_4$ was added. The mixture was stirred vigorously for 15 min then filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 75:25 to 70:30) afforded the title compound **3d** as a clear oil (774 mg, 90%).

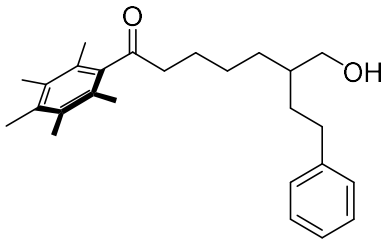
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.31 – 7.24 (2H, m), 7.22 – 7.15 (3H, m), 3.54 (2H, br d, *J*=5.2 Hz), 2.71 – 2.56 (4H, m), 2.23 (3H, s), 2.18 (6H, s), 2.08 (6H, s), 1.82 (1H, p, *J*=6.3 Hz), 1.70 (2H, p, *J*=7.2 Hz), 1.51 – 1.32 (4H, m), 1.28 (1H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.2, 140.9, 140.8, 135.5, 133.2 (2 × C), 129.3 (2 × C), 128.5 (2 × C), 127.4 (2 × C), 126.0, 64.9, 45.6, 42.6, 37.9, 30.8, 26.7, 23.6, 17.3 (2 × C), 16.8, 16.1 (2 × C).

HRMS (ESI$^+$) m/z calcd. for $C_{25}H_{35}O_2$ $[M+H]^+$ 367.2632; found at 367.2638, Δ 1.74 ppm.

FTIR (neat) ν/cm^{-1} = 3029, 2359, 1695, 1496, 1454, 1306, 1123, 1042, 911, 737, 701, 649, 621.

6-(hydroxymethyl)-1-(2,3,4,5,6-pentamethylphenyl)-8-Phenyloctan-1-one, 3e



$LiAlH_4$ (103 mg, 2.72 mmol, 1.00 equiv.), methyl 7-oxo-7-(2,3,4,5,6-pentamethylphenyl)-2-phenethylheptanoate **S4e** (1.11 g, 2.72 mmol, 1.00 equiv.) and Et_2O (20 mL) were subjected to **General Procedure E**. The reaction was quenched by sequential dropwise addition of H_2O (0.1 mL), aq. NaOH (15% w/v, 0.1 mL) and H_2O (0.3 mL) at 0 °C. Purification by column chromatography (Pentane:Et_2O, 70:30 to 65:35) afforded the title compound **3e** as a clear oil (654 mg, 63%).

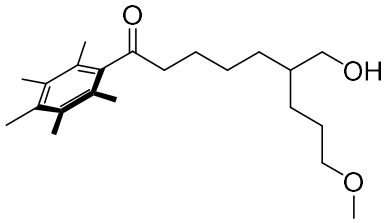
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.34 – 7.23 (2H, m), 7.22 – 7.13 (3H, m), 3.60 (2H, br t, *J*=4.4 Hz), 2.68 (2H, t, *J*=7.4 Hz), 2.65 (2H, t, *J*=8.0 Hz), 2.23 (3H, s), 2.19 (6H, s), 2.10 (6H, s), 1.76 – 1.51 (5H, m), 1.48 – 1.36 (4H, m), 1.27 (1H, br d, *J*=5.4 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.2, 142.7, 140.9, 135.5, 133.2 (2 × C), 128.5 (2 × C), 128.5 (2 × C), 127.4 (2 × C), 125.9, 65.5, 45.7, 40.2, 33.4, 33.0, 30.9, 26.6, 23.7, 17.3 (2 × C), 16.8, 16.1 (2 × C).

HRMS (ESI$^+$) m/z calcd. for $C_{26}H_{36}O_2Na$ $[M+Na]^+$ 403.2608; found at 403.2620, Δ 3.09 ppm.

FTIR (neat) ν/cm^{-1} = 3450, 3026, 2933, 2864, 2360, 1698, 1603, 1496, 1306, 1124, 1030, 913, 643.

6-(hydroxymethyl)-9-Methoxy-1-(2,3,4,5,6-pentamethylphenyl)nonan-1-one, 3f



$LiAlH_4$ (139 mg, 3.67 mmol, 1.00 equiv.), methyl 2-(3-methoxypropyl)-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate **S4f** (1.38 mg, 3.67 mmol, 1.00 equiv.) and Et_2O (20 mL) were subjected to **General Procedure E**. The reaction was quenched by sequential dropwise addition of H_2O (0.14 mL), aq. NaOH (15% w/v, 0.14 mL) and H_2O (0.42 mL) at 0 °C. Purification by column chromatography (Pentane:Et_2O, 70:30 to 40:60) afforded the title compound **3f** as a clear oil (641 mg, 50%).

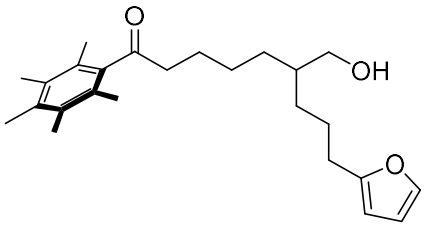
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.59 – 3.50 (2H, m), 3.37 (2H, t, *J*=6.5 Hz), 3.33 (3H, s), 2.68 (2H, t, *J*=7.4 Hz), 2.23 (3H, s), 2.18 (6H, s), 2.09 (6H, s), 1.71 (2H, p, *J*=7.3 Hz), 1.59 (2H, dt, *J*=8.4, 6.6 Hz), 1.55 – 1.20 (7H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.2, 140.9, 135.5, 133.2 (2 × C), 127.4 (2 × C), 73.3, 65.5, 58.7, 45.7, 40.4, 31.0, 27.6, 27.0, 26.6, 23.7, 17.3 (2 × C), 16.8, 16.1 (2 × C).

HRMS (ESI^+) m/z calcd. for $C_{22}H_{37}O_3$ $[M+H]^+$ 349.2737; found at 349.2752, Δ 4.22 ppm.

FTIR (neat) ν/cm^{-1} = 3463, 2933, 2868, 1700, 1577, 1459, 1386, 1306, 1189, 1118, 1042, 917, 871.

9-(furan-2-yl)-6-(hydroxymethyl)-1-(2,3,4,5,6-pentamethylphenyl)Nonan-1-one, 3g



$LiAlH_4$ (23 mg, 0.61 mmol, 1.0 equiv.) was added portionwise to a solution of dimethyl-2-(3-(furan-2-yl)propyl)-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **S4g** (253 mg, 0.61 mmol, 1.00 equiv.) in Et_2O (3 mL) at (–10 °C – 0 °C). The reaction was stirred at (–10 °C – 0 °C) for 6 h. The reaction was quenched by sequential dropwise addition of H_2O (0.2 mL), aq. NaOH (15% w/v, 0.2 mL) and H_2O (1 mL) at 0 °C. Purification by column chromatography (Pentane:Et_2O, 80:20 to 70:30) afforded the title compound **3g** as a colourless oil (130 mg, 55%).

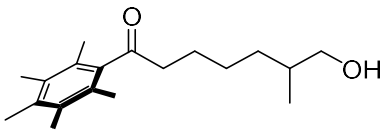
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.29 (1H, dd, *J* = 1.9, 0.9 Hz), 6.28 (1H, dd, *J* = 3.0, 1.9 Hz), 5.98 (dd, *J* = 3.0, 0.9 Hz), 3.55 (2H, d, *J* = 5.5 Hz), 2.68 (2H, t, *J* = 7.4 Hz), 2.62 (2H, t, *J* = 7.1 Hz), 2.23 (3H, s), 2.19 (6H, s), 2.10 (6H, s), 1.77 – 1.60 (4H, m), 1.52 (1H, p, *J* = 5.9 Hz), 1.46 – 1.23 (6H, m).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 212.2, 156.3, 140.9, 140.8, 135.5, 133.2 (2 × C), 127.4 (2 × C), 110.2, 104.9, 65.5, 45.7, 40.3, 30.9, 30.6, 28.4, 26.6, 25.5, 23.7, 17.3 (2 × C), 16.8, 16.1 (2 × C).

HRMS (ESI^+) m/z calcd. for $C_{25}H_{36}O_3Na$ $[M+Na]^+$ 407.2567; found at 407.2557, Δ 2.53 ppm.

FTIR (neat) ν/cm^{-1} = 3431, 2936, 1699, 1597, 1508, 1461, 1403, 1147, 1038, 1008, 918, 796, 738, 639, 625.

7-Hydroxy-6-methyl-1-(2,3,4,5,6-pentamethylphenyl)heptan-1-one, 3h



$LiAlH_4$ (73 mg, 1.92 mmol, 1.00 equiv.), methyl 2-methyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate **S4h** (610 mg, 1.92 mmol, 1.00 equiv.) and Et_2O (15 mL) were subjected to **General Procedure E**. The reaction was quenched by sequential dropwise addition of H_2O (0.07 mL), aq. NaOH (15% w/v, 0.07 mL) and H_2O (0.21 mL) at 0 °C. Purification by column chromatography (Pentane:Et_2O, 70:30 to 65:35) afforded the title compound **3h** as a white solid (441 mg, 79%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.51 (1H, dd, *J*=10.5, 5.8 Hz), 3.43 (1H, dd, *J*=10.5, 6.4 Hz), 2.68 (2H, t, *J*=7.4 Hz), 2.23 (3H, s), 2.18 (6H, s), 2.09 (6H, s), 1.76 – 1.67 (2H, m), 1.67 – 1.59 (1H, m), 1.52 – 1.31 (3H, m), 1.16 (1H, dt, *J*=10.5, 7.9 Hz), 0.92 (3H, d, *J*=6.7 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.2, 140.9, 135.5, 133.2 (2 × C), 127.4 (2 × C), 68.4, 45.7, 35.8, 33.1, 26.7, 23.6, 17.3 (2 × C), 16.8, 16.7 (2 × C), 16.1.

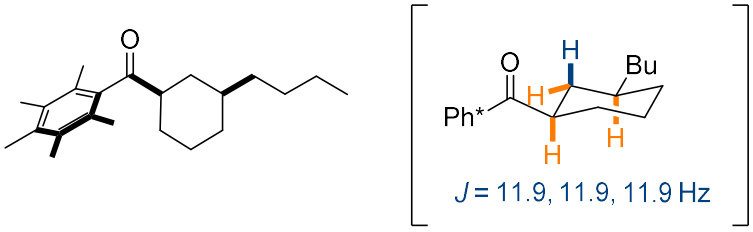
HRMS (ESI^+) m/z calcd. for $C_{19}H_{29}O$ $[M\text{-}OH]^+$ 273.2213; found at 273.2212, Δ 0.37 ppm.

FTIR (neat) ν/cm^{-1} = 3423, 2929, 2870, 1698, 1575, 1461, 1403, 1382, 1304, 1263, 1127, 1096, 1045, 935, 729.

m.p. = 96 – 97 °C.

4.2 Hydrogen Borrowing Cyclisations

((1*R*,3*S*)-3-butylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)Methanone, 4a



From linear regiodefined alcohol: 6-(hydroxymethyl)-1-(2,3,4,5,6-pentamethylphenyl)Decan-1-one **3a** (100 mg, 0.3 mmol, 1.0 equiv.), [R_p,*S*]-PPF-NH_2 (**Ligand 8**) (6.2 mg, 5.0 mol%), Ir(cod)acac (4.8 mg, 4.0 mol%), ^{t}BuOH (0.5 mL, 0.6 M) and KO^{t}Bu (67 mg, 1.2 mmol, 2.0 equiv.) were subjected to **General Procedure A**. Purification by column chromatography (Pentane:Et_2O, 99:1) afforded the title compound **4a** as a white solid (76 mg, 81%, 97:3 e.r., 91:9 d.r.).

From the diol: Pentamethylacetophenone **1** (114 mg, 0.60 mmol), 2-butylpentane-1,5-diol ±**11a** (48 mg, 0.30 mmol), [R_p,*S*]-PPF-NH_2 (**Ligand 8**) (6.2 mg, 5.0 mol%), Ir(cod)acac (4.8 mg, 4 mol%), ^{t}BuOH (0.1 mL, 3 M) and KO^{t}Bu (67 mg, 0.60 mmol, 2.0 equiv.) were subjected to **General Procedure B**. Purification by column chromatography (Pentane:Et_2O, 99:1) afforded the title compound **4a** as a white solid (78 mg, 83%, 86:14 e.r., 92:8 d.r.).

The d.r. was determined by ^{1}H NMR analysis of the isolated product (due to overlapping signals in the crude mixture) through comparison of the C1-H signals: δ 2.65 (1H, tt, *J*=12.0, 3.3 Hz, C1-H, major diastereoisomer) and 2.89 (1H, tt, *J*=8.4, 4.2 Hz, C1-H, minor diastereoisomer). The relative and absolute stereochemistry of the major diastereoisomer was confirmed by X-ray crystallographic analysis after crystallization from deuterated chloroform.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 2.65 (1H, tt, *J*=12.0, 3.3 Hz), 2.24 (3H, s), 2.19 (6H, s), 2.09 (6H, s), 1.99 – 1.87 (2H, m), 1.82 (1H, dp, *J*=13.2, 3.3 Hz), 1.77 – 1.70 (1H, m), 1.35 (1H, qd, *J*=12.7, 3.5 Hz), 1.31 – 1.14 (8H, m), 1.10 (1H, q, *J*=11.9 Hz), 0.92 – 0.79 (4H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 215.1, 140.4, 135.5, 133.2 (2 × C), 128.3 (2 × C), 53.4, 37.4, 37.3, 34.9, 32.7, 29.2, 28.5, 26.0, 23.1, 18.1 (2 × C), 16.9, 16.2 (2 × C), 14.3.

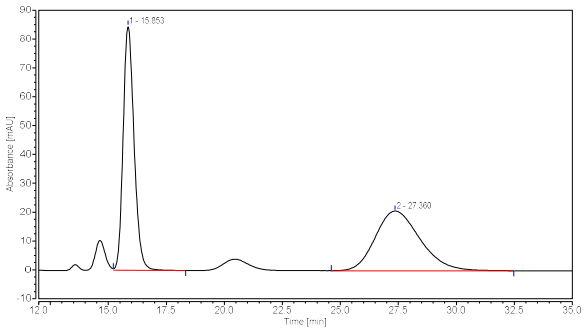
HRMS (ESI^+) m/z calcd. for $C_{22}H_{35}O$ $[M+H]^+$ 315.2682; found at 315.2682 Δ 0.17 ppm.

FTIR (neat) ν/cm^{-1} = 2956, 2926, 2854, 1692, 1574, 1464, 1445, 1381, 1307, 1263, 1155, 1113, 1070, 999, 925, 805, 701.

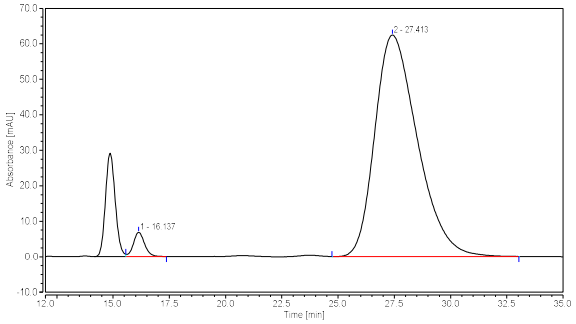
m.p. = 72 – 74 °C.

[α]$_D^{25}$ +12.5 (c = 1.00, $CHCl_3$).

Chiral HPLC: Chiralpak IG with guard, 1% IPA, 99% hexane, 0.7 mL/min, 25 °C, λ = 222 nm, 10 µL injection; τ_R (major) = 27.4 min, τ_R (minor) = 16.1 min. [*N.B.* peaks at 14.6 and 20.5 min correspond to the minor diasteroisomer].

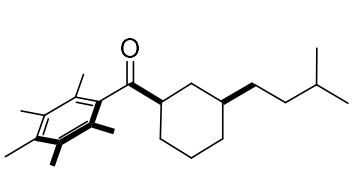


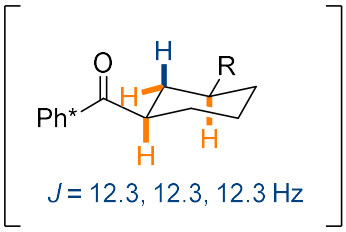
#	Retention Time	Area	Height	Area %
1	15.853	46.355	84.636	50.04
2	27.36	46.279	20.702	49.96



#	Retention Time	Area	Height	Area %
1	16.137	3.944	6.857	2.8
2	27.413	136.844	62.404	97.2

((1*R*,3*R*)-3-isopentylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)Methanone, 4b





6-(hydroxymethyl)-9-methyl-1-(2,3,4,5,6-pentamethylphenyl)decan-1-one **3b** (104 mg, 0.30 mmol, 1.00 equiv.), [R_p,*S*]-PPF-NH_2 (**Ligand 8**) (6.2 mg, 5.0 mol%), Ir(cod)acac (4.8 mg, 4.0 mol%), ^{t}BuOH (0.5 mL, 0.6 M) and KO^{t}Bu (67 mg, 1.2 mmol, 2.0 equiv.) were subjected to **General Procedure A**. Purification by column chromatography (Pentane:Et_2O, 92:8) afforded the title compound **4b** as a white solid (88 mg, 90%, 95:5 e.r., 91:9 d.r.).

The d.r. was determined by ^{1}H NMR analysis of the crude product through comparison of the C1-H signals: δ 2.65 (1H, tt, *J*=11.8, 3.2 Hz, C1-H, major diastereoisomer) and 2.90 (1H, tt, *J*=8.7, 4.1 Hz, C1-H, minor diastereoisomer). The relative stereochemistry of the major diastereomer was determined by J-coupling constants. The absolute stereochemistry of the major diastereoisomer was assigned by analogy.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 2.65 (1H, tt, *J*=12.0, 3.3 Hz), 2.24 (3H, s), 2.19 (6H, s), 2.10 (6H, s), 1.96 (1H, dt, *J*=12.6, 2.6 Hz), 1.94 – 1.88 (1H, m), 1.82 (1H, dp, *J*=13.3, 3.3 Hz), 1.78 – 1.68 (1H, m), 1.52 – 1.42 (1H, m), 1.35 (1H, qd, *J*=12.7, 3.5 Hz), 1.28 – 1.16 (6H, m), 1.11 (1H, q, *J*=12.3 Hz,), 1.88 – 1.84 (7H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 215.1, 140.4, 135.5, 133.2 (2 × C), 128.3 (2 × C), 53.4, 37.8, 36.3, 35.3, 34.9, 32.7, 28.5, 28.4, 26.0, 22.8, 22.8, 18.1 (2 × C), 16.9, 16.2 (2 × C).

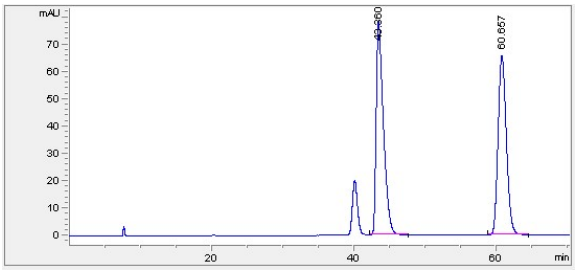
HRMS (ESI^+) m/z calcd. for $C_{23}H_{37}O$ $[M+H]^+$ 329.2839; found at 329.2848, Δ 2.75 ppm.

FTIR (neat) ν/cm^{-1} = 2927, 2853, 2363, 1693, 1449, 1384, 1366, 1309, 1264, 1157, 1089, 999, 926, 799, 760, 702, 652, 618.

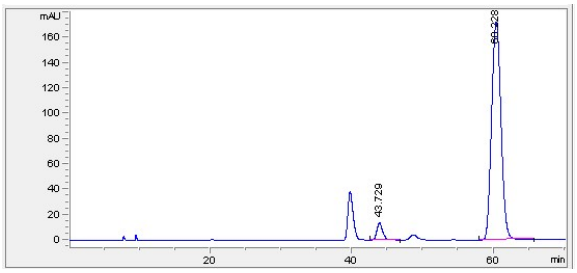
m.p. = 90 °C.

[α]$_D^{25}$ +11.5 (c = 1.00, $CHCl_3$).

Chiral HPLC: Chiralpak IBN-5 with guard, 0.1% IPA, 99.9% hexane, 0.5 mL/min, 25 °C, λ = 230 nm, 10 µL injection; τ_R (major) = 60.2 min, τ_R (minor) = 43.7 min. [*N.B.* peak at 39.3 min correspond to the minor diasteroisomer].

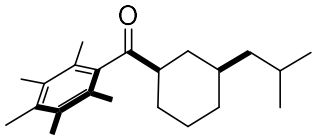


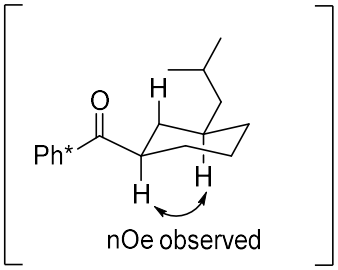
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	43.36	BB	5515.4	79	1.0207	50.808	0.454
2	60.657	BB	5340	65.9	1.2328	49.192	0.803



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	43.729	BB	782.4	13.5	0.8597	4.680	0.76
2	60.228	BB	15934.9	172.1	1.4544	95.320	0.92

((1*R*,3*R*)-3-isobutylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)Methanone, 4c





6-(hydroxymethyl)-8-Methyl-1-(2,3,4,5,6-pentamethylphenyl)nonan-1-one **3c** (101 mg, 0.30 mmol, 1.00 equiv.), [R_p,*S*]-PPF-NH_2 (**Ligand 8**) (6.2 mg, 5.0 mol%), Ir(cod)acac (4.8 mg, 4.0 mol%), ^{t}BuOH (0.5 mL, 0.6 M) and KO^{t}Bu (67 mg, 1.2 mmol, 2.0 equiv.) were subjected to **General Procedure A**. Purification by column chromatography (Pentane:Et_2O, 99:1) afforded the title compound **4c** as a white solid (58 mg, 62%, 92:8 e.r., 91:9 d.r.).

The d.r. was determined by ^{1}H NMR analysis of the isolated product (due to overlapping signals in the crude mixture) through comparison of the C1-H signals: δ 2.66 (1H, tt, *J*=12.1, 3.3 Hz, C1-H, major diastereoisomer) and 2.89 (1H, td, *J*=8.8, 4.3 Hz, C1-H, minor diastereoisomer). The relative stereochemistry of the major diastereomer was determined by nOe analysis. The absolute stereochemistry of the major diastereoisomer was assigned by analogy.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 2.66 (1H, tt, *J*=12.1, 3.3 Hz), 2.24 (3H, s), 2.19 (6H, s), 2.09 (6H, s), 1.99 – 1.85 (2H, m), 1.82 (1H, dp, *J*=13.5, 3.4 Hz), 1.77 – 1.71 (1H, m), 1.70 – 1.62 (1H, m), 1.36 (1H, qd, *J*=12.6, 3.5 Hz), 1.33 – 1.29 (1H, m), 1.24 (1H, qt, *J*=13.1, 3.5 Hz), 1.12 – 1.03 (3H, m), 0.89 – 0.75 (7H, m).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 215.1, 140.4, 135.5, 133.2 (2 × C), 128.3 (2 × C), 53.4, 47.1, 35.1, 35.0, 32.8, 28.5, 26.0, 24.8, 23.3, 22.7, 18.1 (2 × C), 16.9, 16.2 (2 × C).

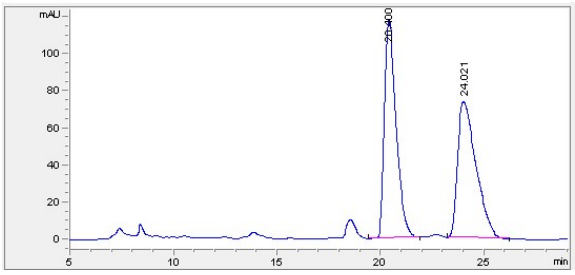
HRMS (ESI^+) m/z calcd. for $C_{22}H_{35}O$ $[M+H]^+$ 315.2682; found at 315.2691, Δ 2.71 ppm.

FTIR (neat) ν/cm^{-1} = 3014, 2953, 2928, 2868, 1694, 1467, 1448, 1384, 1366, 1307, 1262, 1198.

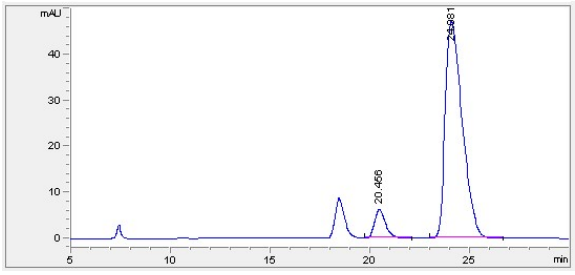
m.p. = 82 – 83 °C.

[α]$_D^{25}$ +11.9 (c = 1.00, $CHCl_3$).

Chiral HPLC: Chiralpak OD with guard, 0.3% IPA, 99.7% hexane, 0.5 mL/min, 25 °C, λ = 230 nm, 10 µL injection; τ_R (major) = 24.1 min, τ_R (minor) = 20.5 min. [*N.B.* peak at 18.4 min corresponds to the minor diasteroisomer].

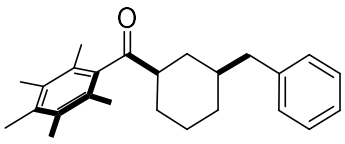


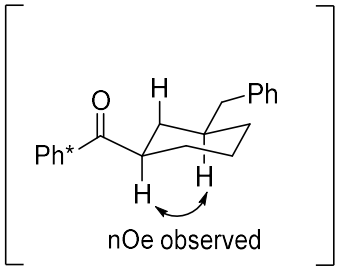
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	20.4	BB	4624.2	117.5	0.601	50.294	0.576
2	24.021	BB	4570.1	73.5	0.9212	49.706	0.461



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	20.456	BB	237.2	6.3	0.5563	7.754	0.699
2	24.081	BB	2822.3	47.8	0.8815	92.246	0.53

((1R,3S)-3-benzylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)Methanone, 4d





From linear regiodefined alcohol: 6-Benzyl-7-hydroxy-1-(2,3,4,5,6-pentamethylphenyl)heptan-1-one **3d** (110 mg, 0.30 mmol, 1.00 equiv.), [R_p,*S*]-PPF-NH_2 (**Ligand 8**) (6.2 mg, 5.0 mol%), Ir(cod)acac (4.8 mg, 4.0 mol%), ^{t}BuOH (0.5 mL, 0.6 M) and KO^{t}Bu (67 mg, 1.2 mmol, 2.0 equiv.) were subjected to **General Procedure A**. Purification by column chromatography (Pentane:Et_2O, 98:2) afforded the title compound **4d** as a white solid (93 mg, 89%, 98:2 e.r., 91:9 d.r.).

From the diol: Pentamethylacetophenone **1** (114 mg, 0.60 mmol), 2-benzylpentane-1,5-diol **±11d** (48 mg, 0.30 mmol), [R_p,*S*]-PPF-NH_2 (**Ligand 8**) (6.2 mg, 5.0 mol%), Ir(cod)acac (4.8 mg, 4 mol%), ^{t}BuOH (0.1 mL, 3 M) and KO^{t}Bu (67 mg, 0.60 mmol, 2.0 equiv.) were subjected to **General Procedure B**. Purification by preparative RP-HPLC (MeCN:H_2O, 60:40 to 100:0) to afford the title compound **4d** as a white solid (73 mg, 70%, 90:10 e.r., 91:9 d.r.).

The d.r. was determined by analytical RP-HPLC of the crude mixture due to overlapping signals in ^{1}H NMR analysis of both the crude and isolated product. The relative and absolute stereochemistry of the major diastereoisomer was confirmed by X-ray crystallographic analysis after crystallization from deuterated chloroform (see Appendix B).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.29 – 7.23 (2H, m), 7.20 – 7.15 (1H, m), 7.14 – 7.09 (2H, m), 2.64 (1H, tt, *J*=12.5, 3.5 Hz), 2.59 (1H, dd, *J*=13.4, 6.4 Hz), 2.48 (1H, dd, *J*=13.3, 7.7 Hz), 2.23 (3H, s), 2.18 (6H, s), 2.08 (6H, s), 2.04 – 1.95 (1H, m), 1.94 – 1.87 (1H, m) 1.80 (1H, dq, *J*=13.6, 3.4 Hz), 1.73 – 1.64 (1H, m), 1.61 – 1.49 (1H, m), 1.38 (1H, qd, *J*=12.9, 3.7 Hz), 1.26 – 1.13 (2H, m), 0.92 (1H, qd, *J*=12.9, 3.7 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 214.8, 140.7, 140.3, 135.5, 133.2 (2 × C), 129.3 (2 × C), 128.3 (2 × C), 128.3 (2 × C), 125.9, 53.2, 44.2, 39.5, 34.7, 32.3, 28.3, 25.8, 18.1 (2 × C), 16.8, 16.1 (2 × C).

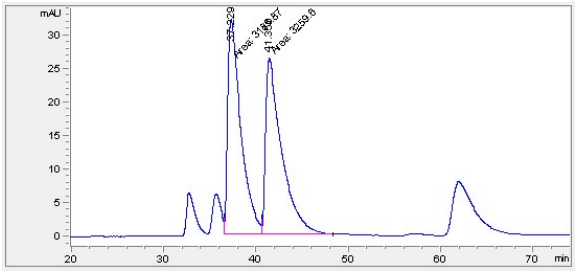
HRMS (ESI^+) m/z calcd. for $C_{25}H_{33}O$ $[M+H]^+$ 349.2526; found at 349.2523, Δ 0.85 ppm.

FTIR (neat) ν/cm^{-1} = 3026, 2928, 2855, 1692, 1496, 1448, 1383, 1309, 1263, 1218, 1174, 1102, 1000, 925, 844, 801, 748, 701, 638, 626, 606.

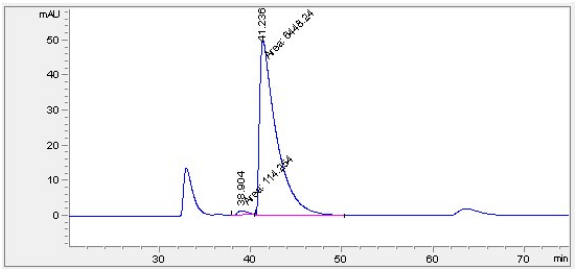
m.p. = 63 °C.

[α]$_D^{25}$ –13.7 (c = 1.00, $CHCl_3$).

Chiral HPLC: Chiralpak IH with guard coupled to OD with guard, 0.5% IPA, 99.5% hexane, 0.7 mL/min, 25 °C, λ = 254 nm, 10 µL injection; τ_R (major) = 41.2 min, τ_R (minor) = 38.9 min. [*N.B.* peaks at 32.7 and 35.6 min correspond to the minor diastereoisomer].

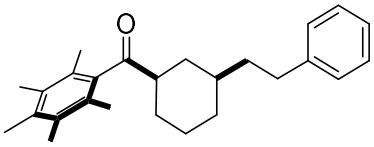


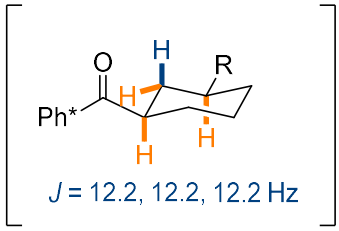
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	37.229	MF	3185.9	32.2	1.6491	49.428	0
2	41.356	FM	3259.6	26.4	2.0573	50.572	0.263



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	38.904	MM	114.3	1.4	1.4044	1.741	0.677
2	41.236	MM	6448.2	50.1	2.1441	98.259	0.237

(2,3,4,5,6-pentamethylphenyl)((1*R*,3*R*)-3-phenethylcyclohexyl)Methanone, 4e





6-(hydroxymethyl)-1-(2,3,4,5,6-pentamethylphenyl)-8-Phenyloctan-1-one **3e** (114 mg, 0.30 mmol, 1.00 equiv.), [R_p,*S*]-PPF-NH_2 (**Ligand 8**) (6.2 mg, 5.0 mol%), Ir(cod)acac (4.8 mg, 4.0 mol%), ^{t}BuOH (0.5 mL, 0.6 M) and KO^{t}Bu (67 mg, 1.2 mmol, 2.0 equiv.) were subjected to **General Procedure A**. Purification by column chromatography (Pentane:Et_2O, 99:1) afforded the title compound **4e** as a white solid (84 mg, 77%, 97:3 e.r., 91:9 d.r.).

The d.r. was determined by analytical RP-HPLC of the crude mixture due to overlapping signals in ^{1}H NMR analysis of both the crude and isolated product. The relative and absolute stereochemistry of the major diastereoisomer was confirmed by X-ray crystallographic analysis after crystallization from deuterated chloroform.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.34 – 7.21 (2H, m), 7.21 – 7.09 (3H, m), 2.71 – 2.51 (3H, m), 2.24 (3H, s), 2.19 (6H, s), 2.10 (6H, s), 2.06 – 1.98 (1H, m), 1.96 – 1.89 (1H, m), 1.88 – 1.79 (2H, m), 1.63 – 1.50 (2H, m), 1.37 (1H, qd, *J*=12.8, 3.3 Hz), 1.32 – 1.20 (2H, m), 1.17 (1H, q, *J*=12.2 Hz), 0.93 (1H, qd, *J*=13.0, 3.9 Hz,).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 215.0, 142.9, 140.3, 135.5, 133.2 (2 × C), 128.5 (2 × C), 128.4 (2 × C), 128.3 (2 × C), 125.8, 53.2, 39.3, 37.0, 34.6, 33.3, 32.6, 28.4, 25.9, 18.1 (2 × C), 16.9, 16.2 (2 × C).

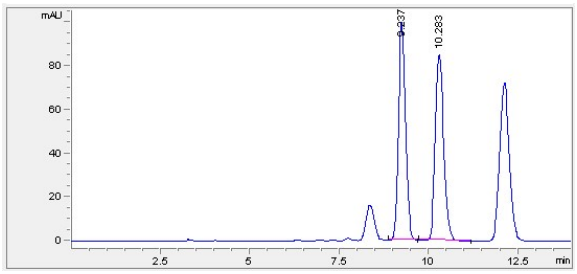
HRMS (ESI^+) m/z calcd. for $C_{26}H_{35}O$ $[M+H]^+$ 363.2682; found at 363.2690 Δ 2.08 ppm.

FTIR (neat) ν/cm^{-1} = 2929, 2855, 1692, 1497, 1454, 1383, 1308, 1263, 1135, 1071, 1001, 927, 749, 700, 637, 627.

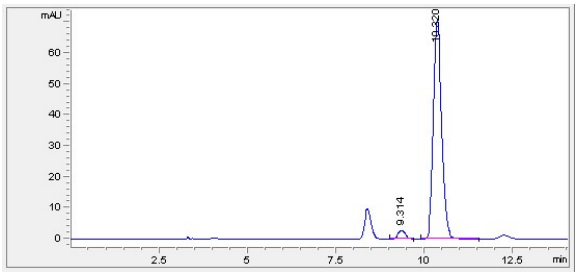
m.p. = 146 – 147 °C.

[α]$_D^{25}$ +19.0 (c = 1.00, $CHCl_3$).

Chiral HPLC: Chiralpak IG with guard, 2% IPA, 98% hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection; τ_R (major) = 10.3 min, τ_R (minor) = 9.3 min. [*N.B.* peak at 8.4 min corresponds to the minor diasteroisomer].

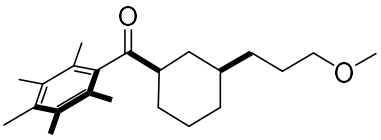


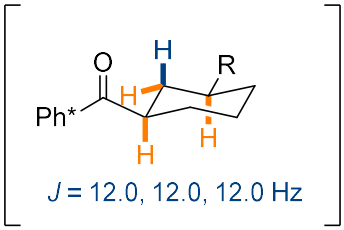
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.237	BB	1399.1	100.4	0.2166	49.857	0.838
2	10.283	BB	1407.2	85.2	0.2566	50.143	0.778



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.314	BB	38.1	2.8	0.215	3.200	0.879
2	10.32	BB	1153.1	70.4	0.2531	96.800	0.796

((1*R*,3*R*)-3-(3-methoxypropyl)cyclohexyl)(2,3,4,5,6-pentamethylphenyl)Methanone, 4f





6-(hydroxymethyl)-9-Methoxy-1-(2,3,4,5,6-pentamethylphenyl)nonan-1-one **3f** (105 mg, 0.30 mmol, 1.00 equiv.), [R_p,*S*]-PPF-NH_2 (**Ligand 8**) (6.2 mg, 5.0 mol%), Ir(cod)acac (4.8 mg, 4.0 mol%), ^{t}BuOH (0.5 mL, 0.6 M) and KO^{t}Bu (67 mg, 1.2 mmol, 2.0 equiv.) were subjected to **General Procedure A**. Purification by column chromatography (Pentane:Et_2O, 92:8) afforded the title compound **4f** as a white solid (78 mg, 79%, 96:4 e.r., 90:10 d.r.).

The d.r. was determined by ^{1}H NMR analysis of the crude product through comparison of the C1-H signals: δ 2.65 (1H, tt, *J*=12.0, 3.3 Hz, C1-H, major diastereoisomer) and 2.91 (1H, td, *J*=8.5, 4.2 Hz, C1-H, minor diastereoisomer). The relative stereochemistry of the major diastereomer was determined by J-coupling constants. The absolute stereochemistry of the major diastereoisomer was assigned by analogy.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.34 (2H, t, *J*=6.9 Hz), 3.32 (3H, s), 2.65 (1H, tt, *J*=12.0, 3.3 Hz), 2.23 (3H, s), 2.18 (6H, s), 2.09 (6H, s), 2.01 – 1.88 (2H, m), 1.83 (1H, dp, *J*=13.0, 3.1 Hz), 1.79 – 1.69 (1H, m), 1.64 – 1.49 (2H, m), 1.36 (1H, qd, *J*=12.7, 3.4 Hz), 1.30 – 1.17 (4H, m), 1.10 (1H, q, *J*=12.0 Hz), 0.93 – 0.80 (1H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 215.0, 140.4, 135.5, 133.2 (2 × C), 128.3 (2 × C), 73.3, 58.7, 53.3, 37.4, 34.8, 33.9, 32.6, 28.4, 27.1, 25.9, 18.1 (2 × C), 16.8, 16.2 (2 × C).

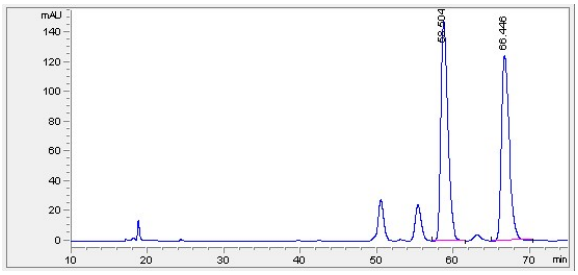
HRMS (ESI^+) m/z calcd. for $C_{22}H_{35}O_2$ $[M+H]^+$ 331.2632; found at 331.2639, Δ 2.23 ppm.

FTIR (neat) ν/cm^{-1} = 2930, 2855, 2362, 1693, 1449, 1308, 1263, 1118, 1001, 928, 802, 762, 703, 640.

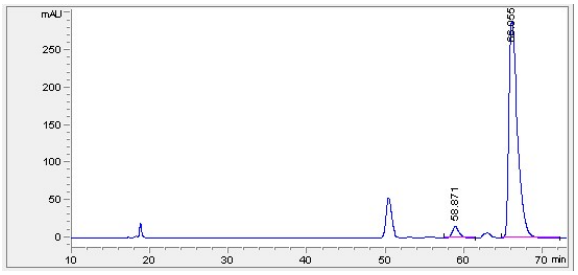
m.p. = 59 °C.

[α]$_D^{25}$ +12.2 (c = 1.00, $CHCl_3$).

Chiral HPLC: Chiralpak IH-IG with guard, 3% IPA, 97% hexane, 0.5 mL/min, 25 °C, λ = 230 nm, 10 µL injection; τ_R (major) = 66.1 min, τ_R (minor) = 58.9 min. [*N.B.* peaks at 50.3 and 55.2 min correspond to the minor diasteroisomer].

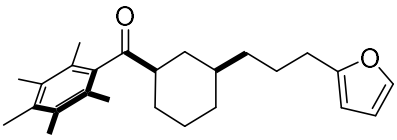


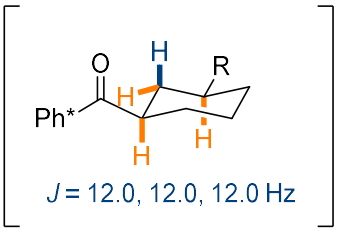
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	58.504	BB	9349.3	147.9	0.9655	50.603	0.623
2	66.446	BB	9126.6	124.8	1.1112	49.397	0.579



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	58.871	BB	1005.5	16.1	0.9223	4.275	0.764
2	66.055	BB	22516.1	291.4	1.1456	95.725	0.442

((1*R*,3*R*)-3-(3-(furan-2-yl)propyl)cyclohexyl)(2,3,4,5,6-pentamethylphenyl)Methanone, 4g





9-(furan-2-yl)-6-(hydroxymethyl)-1-(2,3,4,5,6-pentamethylphenyl)Nonan-1-one **3g** (115 mg, 0.30 mmol, 1.00 equiv.), [R_p,*S*]-PPF-NH_2 (**Ligand 8**) (6.2 mg, 5.0 mol%), Ir(cod)acac (4.8 mg, 4.0 mol%), ^{t}BuOH (0.5 mL, 0.6 M) and KO^{t}Bu (67 mg, 1.2 mmol, 2.0 equiv.) were subjected to **General Procedure A**. Purification by column chromatography (Pentane:Et_2O, 93:7) afforded the title compound **4g** as a white solid (77 mg, 70%, 91:9 e.r., 91:9 d.r.).

The d.r. was determined by ^{1}H NMR analysis of the crude product through comparison of the C1-H signals: δ 2.66 (1H, tt, *J*=12.1, 3.3 Hz, C1-H, major diastereoisomer) and 2.89 (1H, td, *J*=8.5, 4.3 Hz, C1-H, minor diastereoisomer). The relative stereochemistry of the major diastereomer was determined by J-coupling constants. The absolute stereochemistry of the major diastereoisomer was assigned by analogy.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.29 (1H, dd, *J*=1.9, 0.8 Hz), 6.28 (1H, dd, *J*=3.1, 1.9 Hz), 5.98 – 5.94 (1H, m), 2.66 (1H, tt, *J*=12.1, 3.3 Hz), 2.59 (2H, t, *J*=7.5 Hz), 2.25 (3H, s), 2.20 (6H, s), 2.10 (6H, s), 1.97 (1H, dq, *J*=11.3, 2.7 Hz), 1.92 (1H, ddt, *J*=12.7, 3.4, 1.6 Hz), 1.84 (1H, dp, *J*=13.2, 3.3 Hz), 1.79 – 1.72 (1H, m), 1.71 – 1.53 (2H, m), 1.41 – 1.33 (1H, m), 1.33 – 1.18 (4H, m), 1.12 (1H, q, *J*=12.0 Hz), 0.93 – 0.81 (1H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 214.9, 156.5, 140.8, 140.3, 135.5, 133.2 (2 × C), 128.3 (2 × C), 110.2, 104.7, 53.3, 37.3, 37.0, 34.7, 32.6, 28.4, 28.4, 25.9, 25.4, 18.1 (2 × C), 16.8, 16.1 (2 × C).

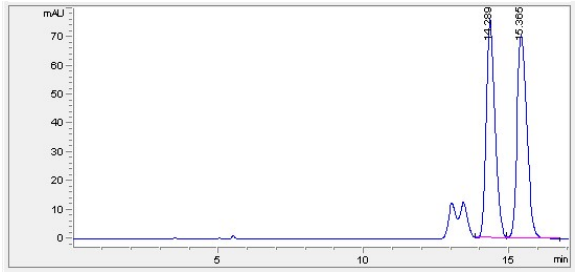
HRMS (ESI^+) m/z calcd. for $C_{25}H_{34}O_2Na$ $[M+Na]^+$ 389.2451; found at 389.2465, Δ 3.58 ppm.

FTIR (neat) ν/cm^{-1} = 2930, 2855, 2360, 1692, 1508, 1448, 1384, 1261, 1074, 924, 800, 732.

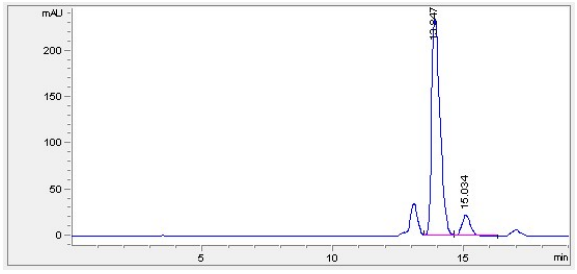
m.p. = 55 – 56 °C.

[α]$_D^{25}$ +9.0 (c = 1.00, $CHCl_3$).

Chiral HPLC: Chiralpak IC with guard, 1% IPA, 99% hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection; τ_R (major) = 13.8 min, τ_R (minor) = 15.0 min. [*N.B.* peaks at 12.5 and 12.9 min correspond to the minor diasteroisomer].

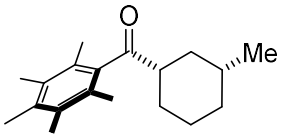


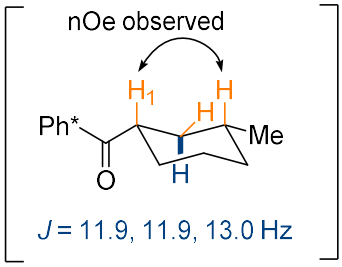
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	14.289	BV	1619.2	76.1	0.3322	49.737	0.724
2	15.365	VB	1636.3	70.2	0.3621	50.263	0.732



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	13.847	VV	5239.4	234.7	0.3425	90.937	0.56
2	15.034	VB	522.2	22.4	0.3585	9.063	0.851

((1*S*,3*R*)-3-methylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)Methanone, 4h





7-Hydroxy-6-methyl-1-(2,3,4,5,6-pentamethylphenyl)heptan-1-one **3h** (87 mg, 0.3 mmol, 1.0 equiv.), (*R*)-DTBM-SEGPHOS (17.7 mg, 5.0 mol%), Ir(cod)acac (4.8 mg, 4.0 mol%), ^{t}BuOH (0.5 mL, 0.6 M) and KO^{t}Bu (67 mg, 1.2 mmol, 2.0 equiv.) were subjected to **General Procedure A**. Purification by column chromatography (Pentane:Et_2O, 99:1) afforded the title compound **4h** as a white solid (70 mg, 86%, 90:10 e.r., 93:7 d.r.).

The d.r. was determined by ^{1}H NMR analysis of the isolated product (due to overlapping signals in the crude mixture) through comparison of the C1-H signals: δ 2.66 (1H, tt, *J*=11.9, 3.2 Hz, C1-H, major diastereoisomer) and 2.85 (1H, tt, *J*=8.6, 4.3 Hz, C1-H, minor diastereoisomer). The relative and absolute stereochemistry of the major diastereoisomer was confirmed by X-ray crystallographic analysis after crystallization from deuterated chloroform.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 2.66 (1H, tt, *J*=11.9, 3.3 Hz), 2.24 (3H, s), 2.19 (6H, s), 2.10 (6H, s), 1.94 – 1.87 (2H, m), 1.81 (1H, dp, *J*=13.1, 3.0 Hz), 1.67 (1H, dtt, *J*=12.7, 3.2, 1.7 Hz), 1.42 – 1.30 (2H, m) 1.25 (1H, qt, *J*= 13.1, 3.2 Hz), 1.10 (1H, dt, *J*=13.0, 11.9 Hz), 0.96 – 0.81 (4H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 215.0, 140.4, 135.5, 133.2 (2 × C), 128.3 (2 × C), 53.4, 36.6, 34.8, 32.6, 28.0, 26.0, 22.8, 18.1 (2 × C), 16.9, 16.2 (2 × C).

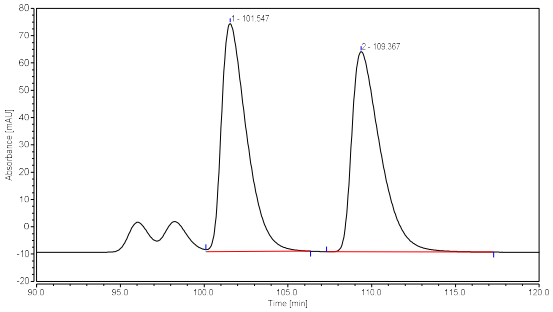
HRMS (ESI^{+}) m/z calcd. for $C_{19}H_{29}O$ $[M+H]^{+}$ 273.2213; found at 273.2212 Δ= 0.37.

FTIR (neat) ν/cm^{-1} = 2923, 2854, 1691, 1456, 1381, 1305, 1265, 1162, 1142, 1110, 1084, 1002, 926, 857, 795, 701.

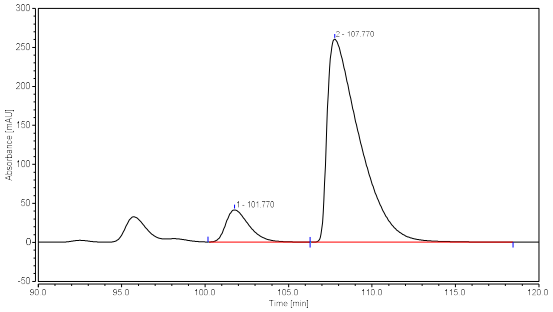
m.p. = 96 – 97 °C.

[α]$_D^{25}$ +10.7 (c = 1.00, $CHCl_3$).

Chiral HPLC: Chiralpak IC-IC-IC with guard, 0.5% IPA, 99.5% hexane, 0.5 mL/min, 5 °C, λ = 254 nm, 10 µL injection; τ_R (major) = 107.8 min, τ_R (minor) = 101.8 min [*N.B.* peaks at 96.0 and 98.3 min correspond to the minor diasteroisomer].

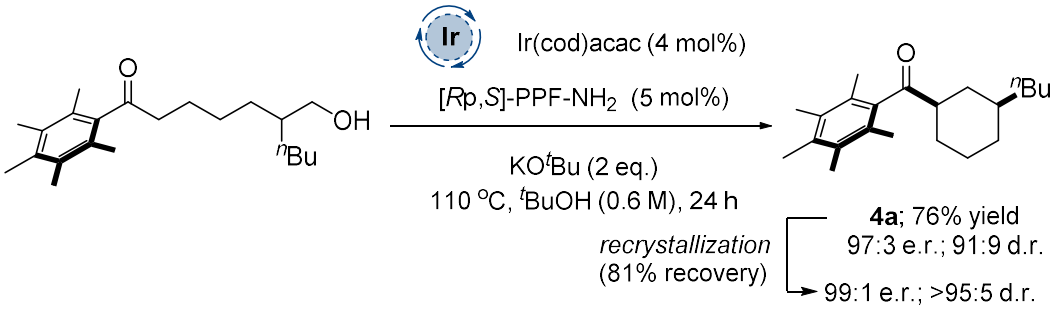


#	Retention Time	Area	Height	Area %
1	101.547	145.631	83.532	50.08
2	109.367	145.149	73.34	49.92



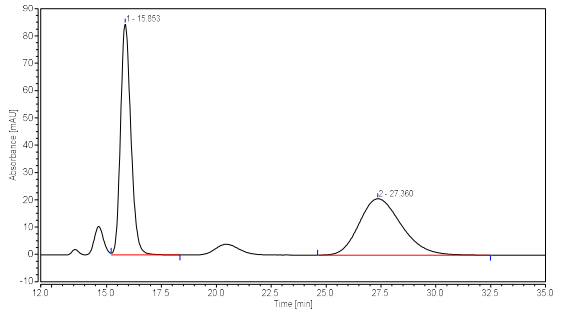
#	Retention Time	Area	Height	Area %
1	101.77	67.455	41.348	10.36
2	107.77	583.496	260.24	89.64

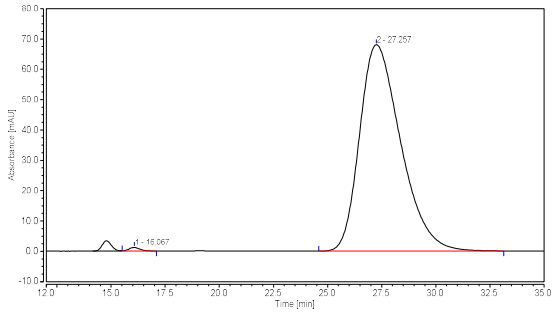
Gram-scale hydrogen borrowing reaction



To a 50 mL ACE pressure tube equipped with a stirrer bar was added linear alcohol **3a** (1.66 g, 5.00 mmol), [R_p,*S*]-PPF-NH_2 (**Ligand 8**) (103 mg, 0.25 mmol), Ir(cod)acac (80 mg, 0.2 mmol) and KO^{t}Bu (1.12 g, 10.0 mmol). The reaction vessel was sealed with a septum then evacuated and backfilled with nitrogen. ^{t}BuOH (8.3 mL, 0.6 M) was purged with nitrogen for 15 min, added to the reaction vessel, septum exchanged for pressure cap and stirred at 110 °C in a preheated oil bath for 24 h. The mixture was cooled to r.t., diluted with Et_2O, filtered through a SiO_2 plug (eluting with ca. 50 mL Et_2O), and concentrated under reduced pressure. Purification by column chromatography (Pentane:Et_2O, 99:1) afforded the title compound **4a** as a white solid (1.20 g, 76%, 97:3 e.r., 91:9 d.r.). Recrystallization from boiling methanol afforded the title compound **4a** as a white needles (968 mg, 81% recovery, 99:1 e.r.; >95:5 d.r.). The spectral data for **4a** was identical to that described above.

Chiral HPLC: Chiralpak IG with guard, 1% IPA, 99% hexane, 0.7 mL/min, 25 °C, λ = 222 nm, 10 µL injection; τ_R (major) = 27.3 min, τ_R (minor) = 16.1 min. [*N.B.* peaks at 14.6 and 20.5 min correspond to the minor diasteroisomer].



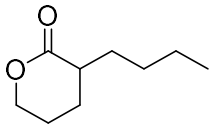


#	Retention Time	Area	Height	Area %
1	15.853	46.355	84.636	50.04
2	27.36	46.279	20.702	49.96

#	Retention Time	Area	Height	Area %
1	16.067	0.685	1.197	0.46
2	27.257	149.939	68.041	99.54

4.3 Synthesis of diols

3-Butyltetrahydro-2H-pyran-2-one, S5



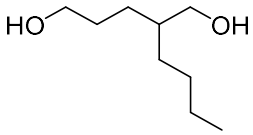
A flame-dried Schlenk tube was charged with disopropylamine (7.73 mL, 54.8 mmol, 1.1 equiv.), dry THF (25 mL) and cooled to –78 °C under Argon. *n*-BuLi in hexanes (35.0 mL, 1.6 M, 55.9 mmol, 1.1 equiv.) was added dropwise, and the resulting solution was stirred for 30 min at –78°C. A solution of commercially available δ-valerolactone (5.00 g, 49.9 mmol, 1.0 equiv.) in dry THF (30 mL) was added dropwise, and stirred for 20 min at –78 °C. A solution of 1-iodobutane (5.68 mL, 49.9 mmol, 1.0 equiv.) and HMPA (8.70 mL, 49.9 mmol, 1.0 equiv.) in dry THF (25 mL) was added dropwise, and the resulting solution was stirred for 10 minutes at –78 °C. The reaction mixture was then warmed to 0 °C and stirred for 4 h. The reaction was quenched by slow addition of sat. aq. NH_4Cl (50 mL) and extracted with CH_2Cl_2 (3 × 80 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo.* Purification by column chromatography (CH_2Cl_2:pentane 40:60 to 60:40) afforded the title compound **S5** as a transparent oil (632 mg, 8%). The spectral data matched that previously reported in the literature.[130]

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 4.35 – 4.24 (2H, m), 2.44 (1H, dtd, *J*=10.8, 7.7, 5.2 Hz), 2.15 – 2.02 (1H, m), 1.98 – 1.80 (3H, m), 1.60 – 1.43 (2H, m), 1.40 – 1.27 (4H, m), 0.94 – 0.85 (3H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 174.9, 68.5, 39.7, 31.1, 29.1, 24.7, 22.8, 22.2, 14.1.

The spectroscopic data was consistent with the literature.[3]

2-Butylpentane-1,5-diol, ±11a



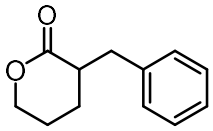
$LiAlH_4$ (172 mg, 4.53 mmol, 1.2 equiv.) was added portionwise to a solution of 3-butyltetrahydro-2H-pyran-2-one **S5** (615 mg, 3.94 mmol, 1.0 equiv.) in Et_2O (25 mL) at 0 °C. The reaction was warmed to r.t. for 1 h. After this time, the reaction was quenched by sequential dropwise addition of H_2O (0.2 mL), aq. NaOH (15% w/v, 0.2 mL) and H_2O (0.6 mL) at 0 °C. The reaction mixture was diluted with Et_2O (10 mL) and $MgSO_4$ was added. The mixture was stirred vigorously for 15 min then filtered and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2:MeOH, 95:5) afforded the title compound **±11a** as a transparent oil (632 g, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.64 (2H, t, *J*=6.4 Hz), 3.58 (1H, dd, *J*=10.7, 5.0 Hz), 3.51 (1H, dd, *J*=10.7, 5.9 Hz), 1.83 (2H, s), 1.66 – 1.54 (2H, m), 1.54 – 1.23 (9H, m), 0.95 – 0.81 (3H, m).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 65.6, 63.3, 40.3, 30.9, 29.9, 29.3, 27.1, 23.2, 14.2.

The spectroscopic data was consistent with the literature.[4]

3-Benzyltetrahydro-2*H*-pyran-2-onemalonate, S6



To a solution of diisopropylamine (4.3 mL, 31.1 mmol) in 25 mL of THF at (0 °C − 10 °C) was added *n*-BuLi (12.4 mL of a 2.5 M solution in hexane, 31.1 mmol, 1.0 equiv.). The solution was stirred for 45 min and cooled to −78 °C. A solution of δ-valerolactone (2.5 mL, 27 mmol, 1.0 equiv.) in 25 mL of THF was added dropwise over 1 h, followed by a solution of benzyl bromide (6.4 mL in 10 mL THF, 54 mmol, 2.0 equiv.). The solution was stirred at −78 °C for 4 h. The reaction was warmed to −10 °C while stirring for 30 min and quenched with 20 mL of saturated aqueous ammonium chloride. The mixture was extracted with Et_2O (3 × 50 mL), dried over $MgSO_4$, and concentrated *in vacuo* to yield a dark yellow oil. Purification by column chromatography (Pentane: Et_2O, 80:20 → 60:40) gave the title compound **S6** as a pale yellow oil (5.76 g, 56%).

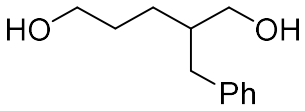
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.33 – 7.26 (2H, m), 7.25 – 7.17 (3H, m), 4.34 – 4.18 (2H, m), 3.41 – 3.30 (1H, m), 2.78 – 2.65 (2H, m), 1.96 – 1.70 (3H, m), 1.59 – 1.42 (1H, m).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 174.1, 139.0, 129.2, 128.5, 126.5, 68.6, 41.5, 37.2, 24.1, 21.9.

HRMS (ESI^+) m/z calcd. for $C_{12}H_{15}O_2$ $[M+H]^+$ 191.1067; found at 191.1069, Δ 1.25 ppm.

The spectroscopic data was consistent with the literature.[5]

Dimethyl-2-benzylpentane-1,5-diol, ±11d



$LiAlH_4$ (0.60 g, 16.0 mmol, 1.80 equiv.) was added portion-wise to a solution of 3-Benzyltetrahydro-2*H*-pyran-2-onemalonate **S6** (4.00 g, 21.0 mmol, 1.00 equiv.) in dry THF (120 mL) at 0 °C. The reaction was stirred at 0 °C for 2 h. The reaction was quenched by sequential dropwise addition of H_2O (3 mL), aq. NaOH (15% w/v, 3 mL) and H_2O (3 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 15 minutes after which Na_2SO_4 was added. The mixture was filtered and concentrated in vacuo. Purification by column chromatography (CH_2Cl_2: MeOH, 98:2 → 93:7) afforded the title compound **±11**d as a colourless oil (3.30 g, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.33 – 7.24 (m, 2H), 7.23 – 7.15 (m, 3H), 3.63 (t, *J* = 6.4 Hz, 2H), 3.58 (dd, *J* = 10.8, 5.2 Hz, 1H), 3.53 (dd, *J* = 10.8, 5.3 Hz, 1H), 2.73 – 2.55 (m, 2H), 1.90 – 1.78 (m, 1H), 1.63 (dtt, *J* = 12.8, 6.5, 3.4 Hz, 2H), 1.53 – 1.35 (m, 4H).

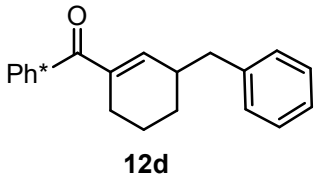
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 140.7, 129.3, 128.5, 126.1, 64.8, 63.2, 42.4, 37.9, 30.0, 26.9.

The spectroscopic data was consistent with the literature.[4]

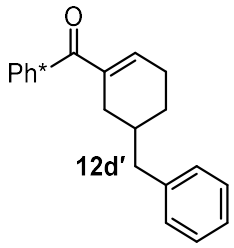
4.4 Mechanistic Experiments

(3-Benzylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone and

(5-Benzylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone (inseparable mixture), 12d, 12d'



12d



2-Benzylpentane-1,5-diol **±11d** (117 mg, 0.600 mmol), Ph* Methyl Ketone **1** (57 mg, 0.30 mmol), $[Ir(cod)Cl]_2$ (2.0 mg, 1.0 mol%) and CataCXium A® (4.3 mg, 4.0 mol%) and KOH (67 mg, 1.2 mmol) were added to a 2-5 mL microwave vial. The vial was sealed, PhMe (1.2 mL, degassed with Ar) was added and the reaction was heated at 115 °C for 24 h. The reaction was cooled to RT, filtered through a silica pad (Et_2O elution) and concentrated *in vacuo*. Purification *via* column chromatography (Pentane/Et_2O, 98:2) afforded a mixture of regioisomers **12d** and **12d'** as a white solid (66.3 mg, 65%, 88:12 r.r.).

Major Regioisomer 12d (from the mixture)

^{1}H NMR (500 MHz $CDCl_3$) δ_H 7.21 (2H, dd, *J*=8.1, 6.4 Hz), 7.18 – 7.13 (1H, m), 7.08 – 6.98 (2H, m), 6.38 (1H, s), 2.66 (1H, m), 2.56 – 2.41 (3H, m), 2.38 – 2.25 (1H, m), 2.25 (3H, s), 2.21 (3H, s), 2.17 (3H, s), 2.03 (3H, s), 1.99 (3H, s), 1.90 – 1.77 (1H, m), 1.70 (1H, m), 1.59 – 1.48 (2H, m), 1.28 (1H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 203.9, 148.6, 140.7, 139.8, 138.2, 135.1, 132.7, 132.6, 129.2, 129.2, 128.3, 126.2, 41.5, 38.4, 27.7, 22.9, 20.7, 17.8, 17.5, 16.8, 16.1.

Selected Characteristic Peaks for the Minor Regioisomer 12d' (from the mixture)

^{1}H NMR (500 MHz $CDCl_3$) δ_H 7.30 (1H, dd, *J*=8.7, 6.6 Hz), 6.48 (1H, t, *J*=2.8 Hz), 2.78 – 2.71 (1H, m), 2.63 – 2.58 (1H, m), 2.23 (3H, s), 1.93 – 1.88 (1H, m)

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 203.5, 145.4, 140.6, 140.3, 138.3, 135.1, 129.3, 128.4, 126.1, 42.9, 35.5, 29.0, 27.5, 26.4, 17.6.

Data for the Regioisomeric Mixture

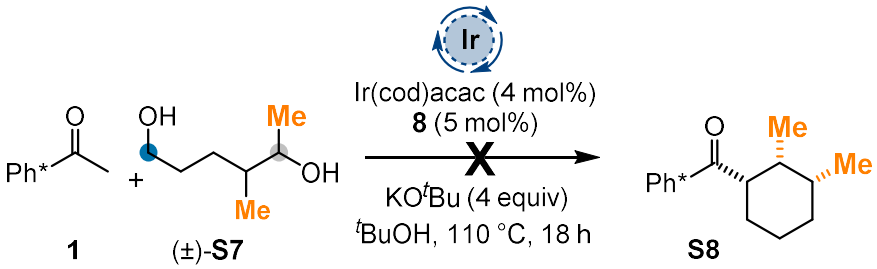
HRMS (ESI^+) m/z calcd. for $C_{25}H_{31}O$ $[M+H]^+$ 347.2369; found at 347.2385, Δ 4.48 ppm.

FTIR (thin film) ν/cm^{-1} = 2932, 2860, 1655, 1634, 1453, 1311, 1272, 1194, 736, 701.

m.p. = 67 – 69 °C.

A solution to the issue of poor regiochemistry illustrated above is to utilize a racemic 1,5-diol that has a primary and a secondary alcohol at the ends; this means that the two equilibrating oxidized species equivalent to **E** & **E'** (see manuscript Scheme 3) would contain an aldehyde and a ketone functionality. We would expect initial C-C bond formation to occur from the aldehyde group and provide a more controlled sequence to the bond formation and thus improve the regioselectivity and the ee of the cyclohexane product. In order to test this hypothesis, dimethylated diol **S7** was prepared and subjected to cyclisation

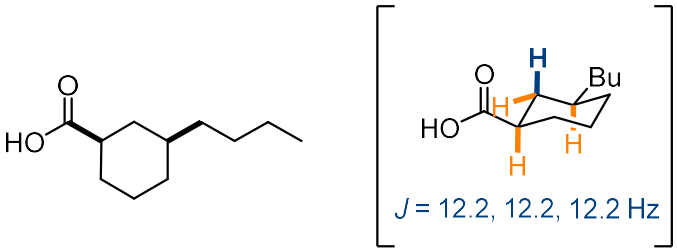
with ketone **1**. However, the extra steric bulk introduced meant that ligand **8** was not effective in promoting cyclisation to form **S8**.



● Initial aldol reaction with **1** should occur here *via* the aldehyde
● Aldol reaction with **1** disfavoured here *via* the ketone

4.5 Derivatisation of Hydrogen Borrowing Products

(1*R*,3*S*)-3-Butylcyclohexane-1-carboxylic acid, 13



((1*R*,3*S*)-3-Butylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone **4a** (63 mg, 0.20 mmol, 99:1 d.r., 99:1 e.r.) was dissolved in CH_2Cl_2 (1.0 mL) and the solution was cooled to –17 °C (ice/salt bath). Br_2 (21 µL, 0.40 mmol) was added dropwise and the resulting solution was stirred at –17 °C for 20 min. The reaction mixture was then warmed to RT, the majority of the volatiles were removed under a stream of nitrogen and the resulting solid was dried *in vacuo* (0.2 mmHg) for 30 sec. The residue was dissolved in THF (1.0 mL), sat. aq. $NaHCO_3$ (1.0 mL) was added and the mixture was stirred at RT for 1 h. The reaction was diluted with CH_2Cl_2 (10 mL) and 3 M HCl (10 mL), the layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (CH_2Cl_2/EtOAc/HCO_2H, 97.95:2:0.05) afforded the title compound **13** as a colourless oil (33.1 mg, 90%, >95:5 d.r.).

^{1}H NMR (400 MHz, MeOD) δ_H 2.26 (1H, tt, *J*=12.1, 3.5 Hz), 2.02 – 1.87 (2H, m), 1.81 (1H, dtd, *J*=9.7, 4.1, 2.3 Hz), 1.75 (1H, dtt, *J*=11.5, 3.4, 1.6 Hz), 1.40 – 1.24 (9H, m), 0.99 (1H, q, *J*=12.2 Hz), 0.93 – 0.74 (4H, m).

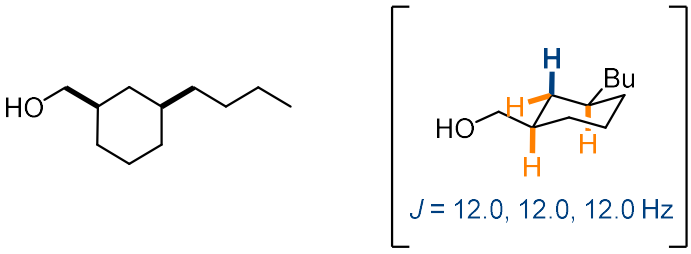
^{13}C NMR (101 MHz, MeOD) δ_C 180.1, 44.7, 38.3, 38.3, 37.0, 33.8, 30.4, 30.2, 26.6, 24.0, 14.4.

HRMS (ESI^-) m/z calcd. for $C_{11}H_{19}O_2$ $[M-H]^-$ 183.1390; found at 183.1382, Δ 4.40 ppm.

FTIR (thin film) ν/cm^{-1} = 3030, 2930, 2857, 1707, 1450, 1421, 1294, 945.

$[\alpha]_D^{25}$ –18.6 (c = 1.00, $CHCl_3$).

((1*R*,3*S*)-3-Butylcyclohexyl)methanol, 14



((1*R*,3*S*)-3-Butylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone **4a** (94 mg, 0.30 mmol, 99:1 d.r., 99:1 e.r.) was dissolved in CH_2Cl_2 (1.5 mL) and the solution was cooled to –17 °C (ice/salt bath). Br_2 (31 µL, 0.60 mmol) was added dropwise and the resulting solution was stirred at –17 °C for 20 min. The reaction mixture was then warmed to RT, the majority of the volatiles were removed under a stream of nitrogen and the resulting solid was dried *in vacuo* (0.2 mmHg) for 30 sec. The residue was dissolved in THF (3 mL) and the resulting stirred solution was cooled to 0 °C. $LiAlH_4$ (57 mg, 1.5 mmol) was added in a single portion and the reaction mixture the reaction was stirred for 1 h at

0 °C. The resulting mixture was diluted with Et_2O (3 mL) and quenched by sequential dropwise addition of H_2O (60 µL), aq. NaOH (15% w/v, 60 µL) and H_2O (180 µL). $MgSO_4$ was added and the resulting suspension was stirred vigorously for 15 min and then filtered and concentrated *in vacuo*. Purification by flash column chromatography (Pentane/Et_2O, 90:10 → 88:12) afforded the title compound **14** as a colourless oil (46.2 mg, 91%).

^{1}H NMR (600 MHz, $CDCl_3$) δ_H 3.50 – 3.32 (2H, m), 1.87 – 1.61 (4H, m), 1.49 (1H, dddt, *J*=15.1, 12.2, 6.3, 3.1 Hz), 1.41 (1H, s), 1.34 – 1.04 (8H, m), 0.91 – 0.85 (3H, m), 0.85 – 0.74 (2H, m), 0.56 (1H, q, *J*=12.0 Hz).

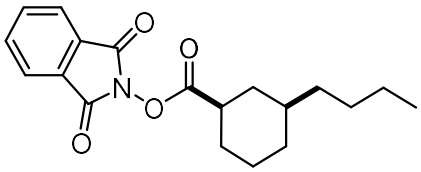
^{13}C NMR (151 MHz, $CDCl_3$) δ_C 69.1, 40.7, 37.5, 37.3, 36.5, 33.5, 29.7, 29.2, 26.0, 23.1, 14.3.

HRMS (ESI$^+$) m/z calcd. for $C_{11}H_{22}ONa$ $[M+Na]^+$ 193.1563; not found.

FTIR (thin film) ν/cm^{-1} = 3349, 2921, 2855, 1466, 1072, 1036, 762, 649.

$[\alpha]_D^{25}$ –2.9 (c = 1.00, $CHCl_3$).

1,3-Dioxoisoindolin-2-yl (1*R*,3*S*)-3-butylcyclohexane-1-carboxylate, 15



((1*R*,3*S*)-3-Butylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone **4a** (63 mg, 0.20 mmol, 99:1 d.r., 99:1 e.r.) was dissolved in CH_2Cl_2 (1.0 mL) and the solution was cooled to –17 °C (ice/salt bath). Br_2 (21 µL, 0.40 mmol) was added dropwise and the mixture was stirred at –17 °C for 20 min. *N*-hydroxyphthalimide (65 mg, 0.40 mmol) and ^{i}Pr$_2$NEt (140 µL, 0.80 mmol) were added sequentially and the reaction was allowed to warm to RT and stirred for 16 h. The mixture was diluted with CH_2Cl_2 (10 mL) and sat. aq. $Na_2S_2O_3$ (10 mL), the layers separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent Pentane/Et_2O, 92:8) gave the title compound **15** as a colourless oil which solidified on standing (52.4 mg, 80%).

^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.88 (2H, dd, *J*=5.5, 3.1 Hz), 7.78 (2H, dd, *J*=5.5, 3.1 Hz), 2.70 (1H, tt, *J*=12.2, 3.5 Hz), 2.24 – 2.08 (2H, m), 1.88 (1H, dp, *J*=13.4, 3.4 Hz), 1.81 – 1.71 (1H, m), 1.52 (1H, qd, *J*=12.8, 3.7 Hz), 1.42 – 1.10 (9H, m), 1.01 – 0.78 (4H, m).

^{13}C NMR (151 MHz, $CDCl_3$) δ_C 172.0, 162.2, 134.8, 129.2, 124.0, 41.1, 37.1, 37.0, 35.4, 32.4, 29.1, 29.1, 25.5, 23.1, 14.2.

HRMS (ESI$^+$) m/z calcd. for $C_{19}H_{23}NO_4Na$ $[M+Na]^+$ 352.1519; found at 352.1513, Δ 1.78 ppm.

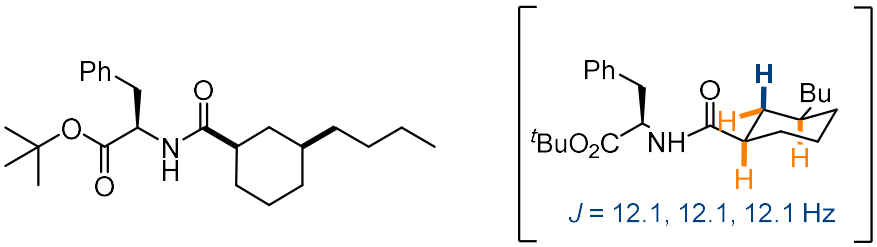
FTIR (thin film) ν/cm^{-1} = 2931, 2858, 1813, 1788, 1747, 879, 698.

m.p. = 33 – 35 °C.

$[\alpha]_D^{25}$ –29.0 (c = 1.00, $CHCl_3$).

N.B. Relative *cis*- stereochemistry assigned by analogy with parent ketone **4a** and other derivatives.

***tert*-Butyl ((1*R*,3*S*)-3-butylcyclohexane-1-carbonyl)-*D*-phenylalaninate, 16**



((1*R*,3*S*)-3-Butylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone **4a** (63 mg, 0.20 mmol, 99:1 d.r., 99:1 e.r.) was dissolved in CH_2Cl_2 (1.0 mL) and the solution was cooled to –17 °C (ice/salt bath). Br_2 (21 µL, 0.40 mmol) was added dropwise and the mixture was stirred at –17 °C for 20 min. D-Phenylalanine *tert*-butyl ester hydrochloride (103 mg, 0.400 mmol) and ^{i}Pr$_2$NEt (140 µL, 0.80 mmol) were added sequentially and the reaction was allowed to warm to RT and stirred for 16 h. The mixture was diluted with EtOAc (10 mL), washed sequentially with 1 M HCl and sat. aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent Pentane/Et_2O, 90:10 → 88:12) gave the title compound **16** as a colourless solid (65.4 mg, 84% >95:5 d.r.).

^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.30 – 7.26 (1H, m), 7.25 – 7.20 (1H, m), 7.17 – 7.10 (2H, m), 5.90 (1H, d, *J*=7.6 Hz), 4.75 (1H, ddd, *J*=7.7, 6.2, 5.5 Hz), 3.20 – 2.88 (2H, m), 2.08 (1H, tt, *J*=12.0, 3.4 Hz), 1.87 (1H, dtt, *J*=12.8, 3.3, 1.9 Hz), 1.80 (2H, dtt, *J*=12.7, 6.5, 2.7 Hz), 1.71 (1H, ddq, *J*=12.9, 3.5, 1.9 Hz), 1.42 (9H, s), 1.35 – 1.28 (1H, m), 1.28 – 1.14 (9H, m), 1.02 (1H, q, *J*=12.1 Hz), 0.91 – 0.86 (3H, m), 0.83 (1H, ddd, *J*=12.6, 11.3, 3.4 Hz).

^{13}C NMR (151 MHz, $CDCl_3$) δ_C 175.5, 171.1, 136.5, 129.8, 128.4, 127.0, 82.5, 53.2, 45.7, 38.2, 37.2, 37.1, 36.1, 32.6, 29.8, 29.1, 28.1, 25.8, 23.1, 14.2;

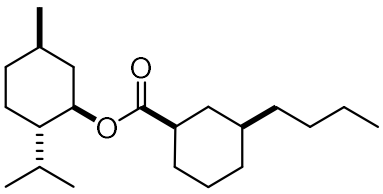
HRMS (ESI$^+$) m/z calcd. for $C_{24}H_{37}NO_3Na$ $[M+Na]^+$ 410.2666; found at 410.2654, Δ 2.90 ppm.

FTIR (thin film) ν/cm^{-1} = 3307, 2928, 2856, 1738, 1650, 1536, 1369, 1158, 760, 701.

m.p. = 51 – 53 °C.

$[\alpha]_D^{25}$ –64.9 (c = 1.00, $CHCl_3$).

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (1*R*,3*S*)-3-butylcyclohexane-1-carboxylate, 17



((1*R*,3*S*)-3-Butylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone **4a** (63 mg, 0.20 mmol, 99:1 d.r., 98:2 e.r.) was dissolved in CH_2Cl_2 (1.0 mL) and the solution was cooled to –17 °C (ice/salt bath). Br_2 (21 µL, 0.40 mmol) was added dropwise and the resulting solution was stirred at –17 °C for 20 min. L-(–)-Menthol (94 mg, 0.60 mmol) was added and the reaction was allowed to warm to RT overnight. The reaction was diluted with CH_2Cl_2 (10 mL) and sat. aq. $Na_2S_2O_3$ (10 mL), the layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column

chromatography (Pentane → Pentane/Et_2O 99.5:0.5) afforded the title compound **17** as a colourless oil (54.5 mg, 85%, >95:5 d.r.).

^{1}H NMR (500 MHz $CDCl_3$), δ_H 4.65 (1H, td, *J*=10.9, 4.4 Hz), 2.25 (1H, tt, *J*=12.0, 3.5 Hz), 1.99 – 1.82 (4H, m), 1.82 – 1.75 (1H, m), 1.75 – 1.62 (3H, m), 1.48 (1H, ddtd, *J*=15.1, 12.7, 6.6, 3.2 Hz), 1.43 – 1.17 (10H, m), 1.10 – 0.78 (14H, m), 0.75 (3H, d, *J*=7.0 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 176.0, 73.7, 47.2, 44.1, 41.1, 37.2, 37.2, 35.8, 34.5, 32.7, 31.5, 29.3, 29.2, 26.3, 25.7, 23.5, 23.1, 22.2, 21.0, 16.4, 14.3.

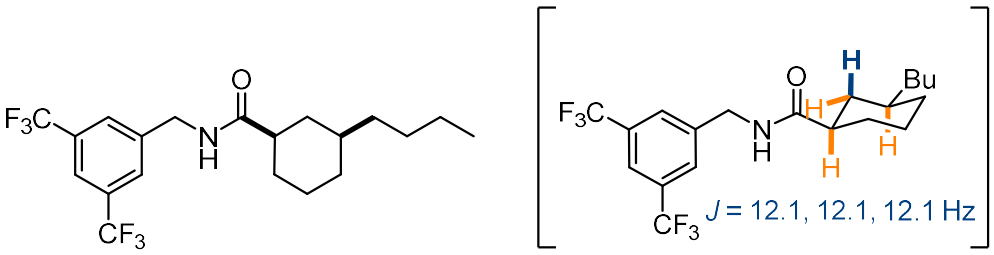
HRMS (ESI^+) m/z calcd. for $C_{21}H_{38}O_2$ $[M+H]^+$ 323.2945; found at 323.2941, Δ 1.03 ppm.

FTIR (thin film) ν/cm^{-1} = 2956, 2930, 2857, 1731, 1458, 1201, 1175, 1139, 1099.

$[\alpha]_D^{25}$ –57.8 (c = 1.00, $CHCl_3$).

N.B. Relative *cis*- stereochemistry assigned by analogy with parent ketone **4a** and other derivatives.

(1*R*,3*S*)-*N*-(3,5-bis(trifluoromethyl)benzyl)-3-Butylcyclohexane-1-carboxamide, 18



((1*R*,3*S*)-3-Butylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone **4a** (63 mg, 0.20 mmol, 99:1 d.r., 98:2 e.r.) was dissolved in CH_2Cl_2 (1.0 mL) and the solution was cooled to –17 °C (ice/salt bath). Br_2 (21 µL, 0.40 mmol) was added dropwise and the resulting solution was stirred at –17 °C for 20 min. (3,5-bis(trifluoromethyl)phenyl)methanamine (146 mg, 0.600 mmol) was added and the reaction was allowed to warm to RT overnight. The reaction was diluted with EtOAc (10 mL) and sat. aq. $Na_2S_2O_3$ (10 mL), the layers were separated and the aqueous phase extracted with EtOAc (3 × 15 mL). The combined organic phases were washed sequentially with 3 M HCl and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (Pentane/EtOAc, 90:10) afforded the title compound **18** as a white solid (63.9 mg, 78%, >95:5 d.r.).

^{1}H NMR (400 MHz $CDCl_3$) δ_H 7.77 (1H, s), 7.70 (2H, s), 5.99 (1H, t, *J*=6.1 Hz), 4.55 (2H, d, *J*=6.1 Hz), 2.18 (1H, tt, *J*=12.0, 3.4 Hz), 1.98 – 1.79 (3H, m), 1.74 (1H, dtt, *J*=12.7, 3.2, 1.6 Hz), 1.48 – 1.34 (1H, m), 1.34 – 1.17 (8H, m), 1.11 (1H, q, *J*=12.1 Hz), 0.94 – 0.81 (4H, m).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C δ 176.5, 141.6, 132.2 (q, $^2J_{CF}$ = 32.7 Hz), 127.7 (q, $^3J_{CF}$ = 3.4 Hz), 124.7 (q, $^1J_{CF}$ = 273.4 Hz), 122.0, 121.5 (apparent p, $^3J_{CF}$ = 3.8 Hz), 45.7, 42.5, 37.3, 37.1, 36.4, 32.6, 29.8, 29.1, 25.7, 23.1, 14.2.

^{19}F NMR (377 MHz, $CDCl_3$) δ_F -62.7.

HRMS (ESI^+) m/z calcd. for $C_{20}H_{25}F_6NONa$ $[M+Na]^+$ 432.1733; found at 432.1729, Δ 0.94 ppm.

FTIR (thin film) ν/cm^{-1} = 3289, 2930, 2857, 1649, 1547, 1382, 1284, 1179, 1133.

m.p. = 89 – 91 °C.

$[\alpha]_D^{25}$ –5.0 (c = 1.00, $CHCl_3$).

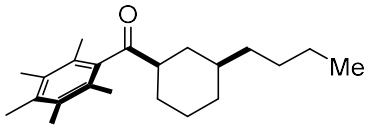
5. References

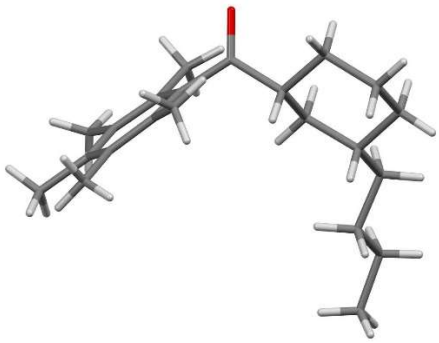
1. A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen and F. J. Timmers, *Organometallics*, 1996, **15**, 1518-1520.
2. W. M. Akhtar, R. J. Armstrong, J. R. Frost, N. G. Stevenson and T. J. Donohoe, *J. Am. Chem. Soc.* , 2018, **140**, 11916-11920.
3. A. Petti, M. C. Leech, A. D. Garcia, I. C. A. Goodall, A. P. Dobbs and K. Lam, *Angewandte Chemie International Edition*, 2019, **58**, 16115-16118.
4. T. Kano, F. Shirozu, M. Akakura and K. Maruoka, *Journal of the American Chemical Society*, 2012, **134**, 16068-16073.
5. E. E. Kwan, J. R. Scheerer and D. A. Evans, *The Journal of Organic Chemistry*, 2013, **78**, 175-203.
6. M. E. Kuehne, W. G. Bornmann, I. Markó, Y. Qin, K. L. LeBoulluec, D. A. Frasier, F. Xu, T. Mulamba, C. L. Ensinger, L. S. Borman, A. E. Huot, C. Exon, F. T. Bizzarro, J. B. Cheung and S. L. Bane, *Organic & Biomolecular Chemistry*, 2003, **1**, 2120-2136.

6. X-Ray Crystallography Data

Single crystal X-ray diffraction experiments were performed on a (Rigaku) Oxford Diffraction Supernovae A diffractometer using Cu-K_α radiation (λ = 1.54184 Å) and a graphite monochromator. Samples were mounted on perfluoropoly-ethyl ether oil and cooled by a Cryostream N_2 open-flow cooling device to 150 K throughout the data collection process. The diffraction patterns were integrated and reduced using the software CrysAlisPro. The software CRYSTALS for Microsoft Windows was used to obtain ab initio solutions (using SuperFlip embedded within CRYSTALS) and carry out structure refinement.

X-ray Crystallographic data for 4a: ((1*R*,3*S*)-3-Butylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone

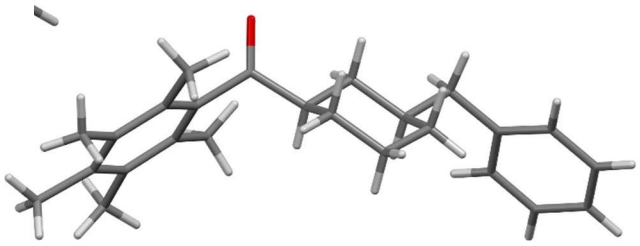




Empirical formula	C22 H34 O	
Formula weight	314.51	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system / Space group	Orthorhombic /	P 2_1 2_1 2_1
Unit cell dimensions	a = 5.38770(10) Å	α= 90°.
	b = 16.7335(4) Å	β= 90°.
	c = 21.1766(5) Å	γ = 90°.
Volume	1909.18(7) $Å^3$	
Z	4	
Density (calculated)	1.094 Mg/m^3	
Absorption coefficient	0.483 mm^{-1}	
F(000)	696	
Crystal size	0.28 x 0.05 x 0.02 mm^3	
Theta range for data collection	4.175 to 76.254°.	
Index ranges	-6<=h<=6, -17<=k<=20, -26<=l<=24	
Reflections collected	20127	
Independent reflections	3971 [R(int) = 0.038]	

Completeness to theta = 76.254°	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.99 and 0.83
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3971 / 0 / 209
Goodness-of-fit on F^2	0.9979
Final R indices [I>2sigma(I)]	R1 = 0.0350, wR2 = 0.0914
R indices (all data)	R1 = 0.0398, wR2 = 0.0957
Absolute structure parameter	0.11(12)
Largest diff. peak and hole	0.23 and -0.20 e.$Å^{-3}$

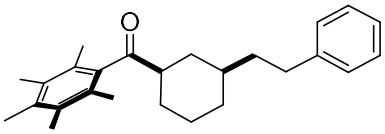
X-ray Crystallographic data for 4d: ((1*R*,3*S*)-3-Benzylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone

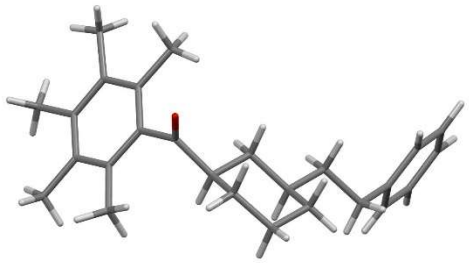


Empirical formula	C25 H32 O	
Formula weight	348.53	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system / Space group	Monoclinic /	P 2_1
Unit cell dimensions	a = 17.8980(4) Å	α= 90°.
	b = 10.75260(10) Å	β= 116.475(2)°.
	c = 17.9306(3) Å	γ = 90°.
Volume	3088.86(11) $Å^3$	
Z	6	
Density (calculated)	1.124 Mg/m^3	
Absorption coefficient	0.500 mm^{-1}	
F(000)	1140	
Crystal size	0.38 x 0.26 x 0.02 mm^3	

Theta range for data collection	4.689 to 76.287°.
Index ranges	-22<=h<=22, -13<=k<=13, -22<=l<=21
Reflections collected	66937
Independent reflections	12801 [R(int) = 0.046]
Completeness to theta = 76.287°	99.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.99 and 0.68
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	12801 / 1 / 704
Goodness-of-fit on F^2	1.0031
Final R indices [I>2sigma(I)]	R1 = 0.0397, wR2 = 0.1018
R indices (all data)	R1 = 0.0452, wR2 = 0.1082
Absolute structure parameter	-0.07(9)
Largest diff. peak and hole	0.26 and -0.16 e.Å-3

X-ray Crystallographic data for 4e: (2,3,4,5,6-Pentamethylphenyl)((1*R*,3*R*)-3-phenethylcyclohexyl)methanone

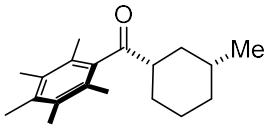


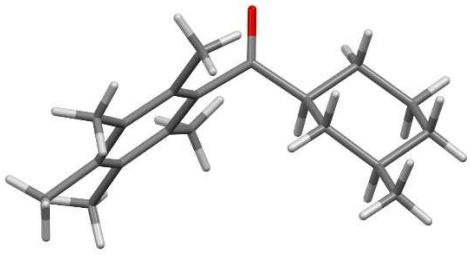


Empirical formula	C26 H34 O	
Formula weight	362.56	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system /Space group	Orthorhombic /	P 2_1 2_1 2_1
Unit cell dimensions	a = 5.58060(10) Å	α = 90°.
	b = 11.9554(2) Å	β= 90°.
	c = 31.1944(4) Å	γ = 90°.
Volume	2081.24(6) $Å^3$	
Z	4	
Density (calculated)	1.157 Mg/m^3	

Absorption coefficient	0.512 mm^{-1}
F(000)	792
Crystal size	0.20 x 0.18 x 0.03 mm^3
Theta range for data collection	3.960 to 76.165°.
Index ranges	-6<=h<=6, -12<=k<=14, -38<=l<=39
Reflections collected	48092
Independent reflections	4317 [R(int) = 0.049]
Completeness to theta = 74.642°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.98 and 0.84
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4317 / 0 / 245
Goodness-of-fit on F^2	1.0029
Final R indices [I>2sigma(I)]	R1 = 0.0323, wR2 = 0.0862
R indices (all data)	R1 = 0.0350, wR2 = 0.0888
Absolute structure parameter	0.04(9)
Largest diff. peak and hole	0.09 and -0.07 e.Å-3

X-ray Crystallographic data for 4h: ((1*S*,3*R*)-3-Methylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone





Empirical formula	C19 H28 O	
Formula weight	272.43	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system / Space group	Monoclinic /	$P\ 2_1$
Unit cell dimensions	a = 8.4471(3) Å	α= 90°.
	b = 21.8813(8) Å	β= 102.958(4)°.
	c = 8.9494(4) Å	γ = 90°.

Volume	1612.03(11) Å3
Z	4
Density (calculated)	1.122 Mg/m^3
Absorption coefficient	0.504 mm^{-1}
F(000)	600
Crystal size	0.19 x 0.18 x 0.05 mm3
Theta range for data collection	4.041 to 76.270°.
Index ranges	-10<=h<=10, -27<=k<=27, -11<=l<=8
Reflections collected	15834
Independent reflections	6614 [R(int) = 0.046]
Completeness to theta = 73.982°	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.98 and 0.49
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6612 / 1 / 362
Goodness-of-fit on F^2	1.0038
Final R indices [I>2sigma(I)]	R1 = 0.0657, wR2 = 0.1629
R indices (all data)	R1 = 0.0742, wR2 = 0.1804
Absolute structure parameter	0.0(2)
Largest diff. peak and hole	0.07 and -0.06 $e.Å^{-3}$

7. Computational Data

Calculations Supporting Information

Computational Details

All calculations were performed using ORCA 5.0.3 program suite.[1] Relaxed scans of hydride transfer reaction coordinates were performed using the B97-3c composite method.[2] Geometry optimizations and frequency calculations were performed with the range-separated ωB97X hybrid exchange–correlation functional[3] including the D3BJ empirical dispersion correction[4] and the double-ζ def2-SVP basis set.[5] Single point energy refinements were performed with the larger quadruple-ζ def2-QZVP basis set. The resolution of identity (RI-J) approximation[6] was used to speed up Coulomb integral evaluation with the def2/J auxiliary basis set,[8] while Hartree–Fock exchange integrals were approximated using the chain-of-spheres algorithm.[9] Solvent effects of *t*-BuOH were accounted for by the conductor-like polarizable continuum model (C-PCM).[10] Since *t*-BuOH is not available as a default solvent, we manually included its parameters, using a dielectric constant of 12.47 and a refractive index of 1.3878 as reported by Truhlar.[11]

"VeryTightSCF" and "TightOpt" convergence criteria (10^{-9} Ha tolerance for orbitals and 10^{-6} Ha tolerance for optimization step) were employed together with defgrid3. Geometries of intermediates and transition states (TSs) were optimized to minima and first-order saddle points on the potential energy surface (PES), respectively. The nature of the optimized stationary points was confirmed by analytic calculation of vibrational frequencies. Intrinsic reaction coordinate (IRC) calculations[12] were performed to verify the connectivity of the stationary points along the minimum energy path (MEP) of each calculated reaction path.

Calculated Gibbs' free energies were readjusted using our laboratory's otherm code[13] to 383.15 K and 1 M standard state employing the quasi-rigid-rotor–harmonic-oscillator (qRRHO) method of Grimme[14] to correct for overestimation of entropy contributions of anharmonic low-frequency vibrations below 100 cm^{-1}. Natural population analyses were carried out with the NBO7 program,[15] and non-covalent interactions

(NCIs) were calculated with the NCIPLOT 4.2 program[16] using promolecular electron densities. All calculations are publicly available as a dataset collection from the ioChem-BD repository[17] (https://doi.org/10.19061/iochem-bd-6-399).

Reaction Energetics

The initial hydrogen atom transfer (HAT) reaction from Ir–H to the enone can proceed *via* eight distinct configurations, illustrated in Figure SX1. These depend on i) the relative position of the NH_2 or PPh_2 group of the chiral ligand to the migrating H (*cis* / *trans*), ii) The coordination of the Ir center to the substrate (*Re* / *Se* face), and iii) the substrate isomeric form ((*R*)- or (*S*)-isomer). For each of these configurations, the respective TSs were attempted optimized.

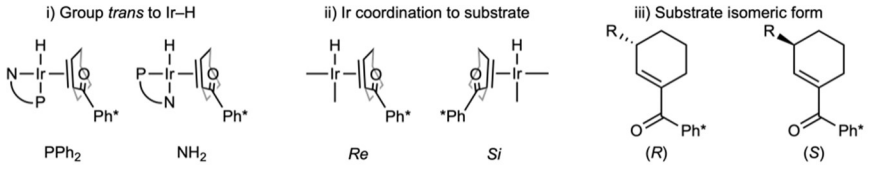


Figure SX1. Possible configurations for the reactive Ir-complex–enone system. i) the group of the chiral bidentate ligand located *trans* to the Ir–H, ii) enone face to which Ir coordinates, and iii) the isomeric form of the enone substrate.

For the four configurations with the NH_2 group *trans* to Ir–H, no TS was found. Therefore, relaxed scans along the H transfer coordinate were performed for these four structures, using R = Me, revealing a continuous increase in energy as the C–H bond shortened and no product minimum could be identified (Figure SX2). The non-reactive nature of this configuration is attributed to the lower *trans* effect of NH_2 compared to PPh_2, rendering the Ir–H bond intact. In contrast, for the other four configurations with PPh_2 *trans* to Ir–H, all stationary points along the reaction path were identified. The activation barriers for R = Me and R = Bu are summarized in Table SX1, and the reaction profile for R = Me shown in Figure SX3 (see Figure X1 in the main text for the R = Bu profile). For notational simplicity, the reactive configurations with PPh_2 *trans* to Ir–H are simply labeled by the enone face to which Ir coordinates (*Re* or *Si*) and the enone isomer ((*R*) or (*S*)).

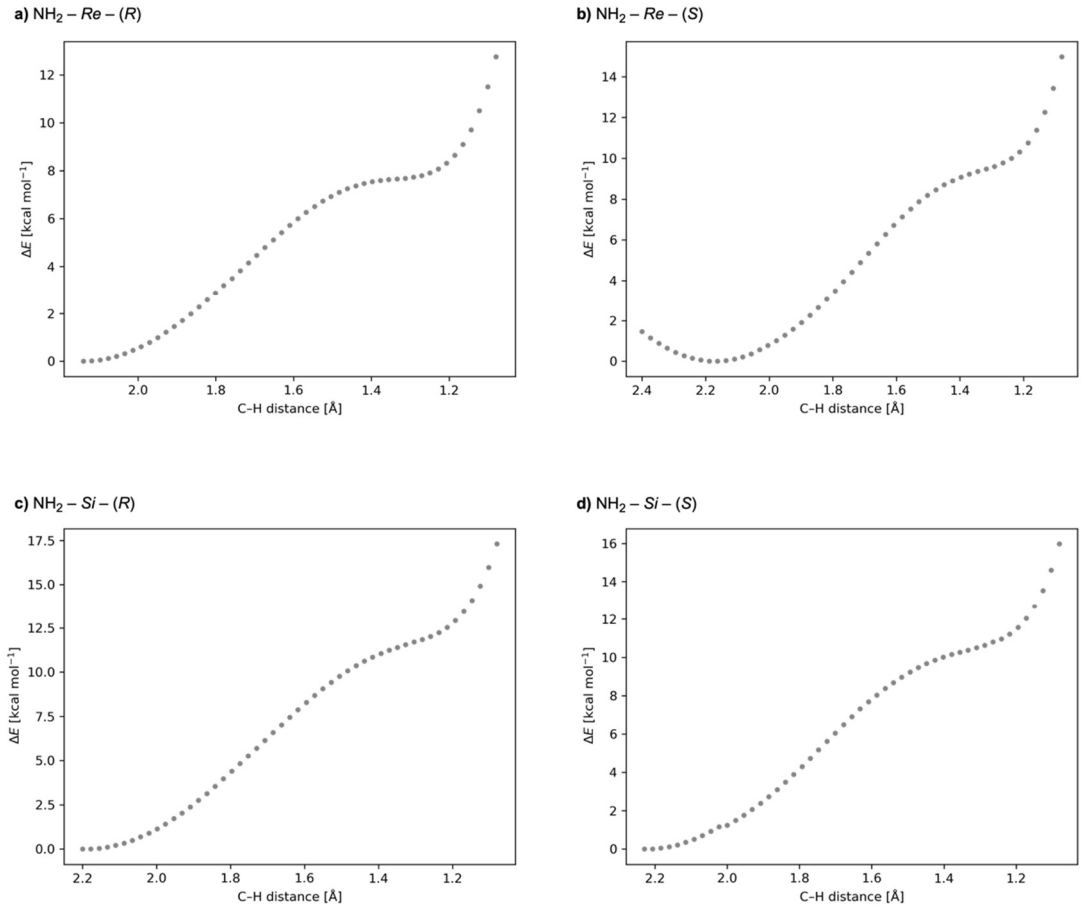


Figure SX2. Relaxed scans performed at the B97-3c level of theory along the H transfer coordinate for R = Me for the four different configurations with NH_2 *trans* to Ir–H: a) NH_2 – *Re* – (*R*), b) NH_2 – *Re* – (*S*), c) NH_2 – *Si* – (*R*), and d) NH_2 – *Si* – (*S*). All energies are given in kcal mol^{-1} relative to the lowest-energy structure along each relaxed scan.

Table SX1. Calculated barriers for the initial hydrogen atom transfer (HAT) from Ir–H to the enone and the subsequent coordination-change step, from η^1-to-η^3 coordination, for R = Me and R = Bu. The configurations are those illustrated in Figure SX1. All energies are given in kcal mol^{-1} relative to the lowest-energy reactant complex (*i.e.*, the *Re* – (*R*) reactant complex).

Configuration	$\Delta G^{\ddagger}$ [kcal mol^{-1}]			
	R = Me HAT	R = Me η^1-to-η^3	R = Bu HAT	R = Bu η^1-to-η^3
NH_2 – *Re* – (*R*)	—	—	—	—
NH_2 – *Re* – (*S*)	—	—	—	—
NH_2 – *Si* – (*R*)	—	—	—	—
NH_2 – *Si* – (*S*)	—	—	—	—
Re – (*R*)	2.3	8.1	2.5	8.2
Re – (*S*)	4.2	7.7	4.7	5.8
Si – (*R*)	5.6	0.2	6.5	4.2
Si – (*S*)	4.0	1.3	4.5	1.8

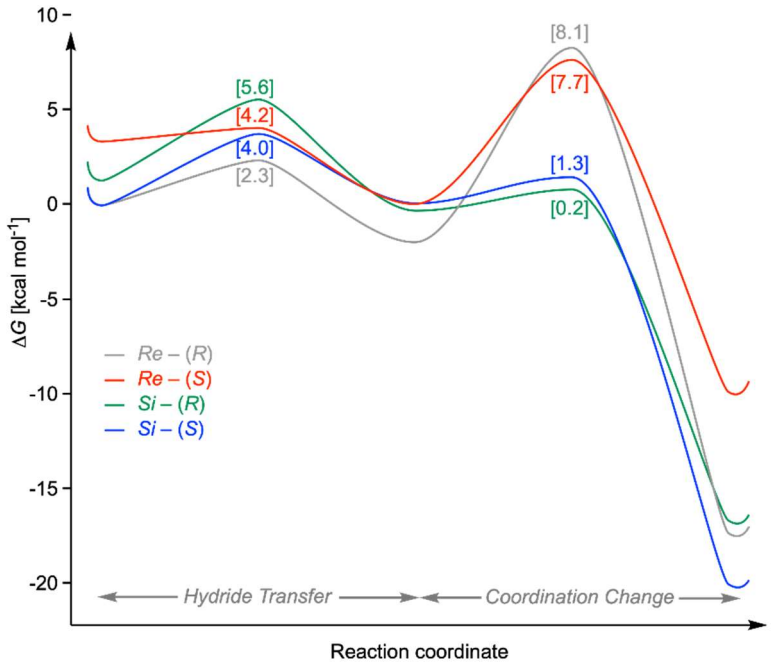


Figure SX3. Energy profile computed at the ωB97X-D3BJ/def2-QZVP level of theory for the two-step reaction involving hydride transfer from Ir–H to the enone and η^1-to-η^3 coordination change for R = Me. The gray, red, green and blue lines indicate the free energies along the reaction path for the *Re* – (*R*), *Re* – (*S*), *Si* – (*R*) and *Si* – (*S*) configurations, respectively. Free energies are given in brackets at each TS in kcal mol^{-1} relative to the lowest-energy reactant complex (*i.e.*, the *Re* – (*R*) reactant complex).

Calculation of Enantiomeric Ratios

The enantiomeric ratio (er) for each configuration, er_i, was calculated using the Boltzmann average according to

$$\mathrm{er}_i = \frac{\exp\left(-\Delta G_i^{\ddagger}(RT)^{-1}\right)}{\sum_j \exp\left(-\Delta G_j^{\ddagger}(RT)^{-1}\right)} \times 100, \quad (1)$$

where $\Delta G^{\ddagger}$ is the rate-determining barrier for a given configuration, R = 1.987e-3 kcal K^{-1} mol^{-1} is the gas constant and T = 383.15 K is the temperature. The summation is performed over all configurations, j = *Re* – (*R*), *Re* – (*S*), *Si* – (*R*), *Si* – (*S*). The overall er for the (*R*) and (*S*) products was obtained by summing together the individual contributions of the configurations yielding the (*R*) and (*S*) products, respectively. This resulted in computed er in favor of the (*S*) product of 94:6 and 89:11 for R = Bu and R = Me, respectively.

Table SX2. $\Delta G^{\ddagger}$ values used in the calculation of enantiomeric ratios along with calculated contributions of each configuration.

Configuration	R = Bu		R = Me	
	$\Delta G^{\ddagger}$ [kcal mol^{-1}]	er_i	$\Delta G^{\ddagger}$ [kcal mol^{-1}]	er_i
Re – (*R*)	8.2	0.6	8.1	0.4
Re – (*S*)	5.8	13.8	7.7	0.7
Si – (*R*)	6.5	5.8	5.6	11.0
Si – (*S*)	4.5	79.7	4.0	87.9

Transition State Structures

To further rationalize the differences in energies, we analyzed the structures' geometric parameters and natural charges for the HAT step, with R = Bu (Figure SX4 and Table SX3). All four hydride transfer TSs show similar interatomic distances, with the *Re* – (*R*) TS exhibiting a slightly earlier TS geometry than the other configurations. Indeed, *Re* – (*R*) has the lowest barrier (2.5 kcal mol^{-1}). Conversely, the *Si* – (*R*) configuration has the latest TS and the highest barrier (6.5 kcal mol^{-1}). These results are consistent with Hammond's postulate. As for the calculated atomic charges, these are all within 0.02 *e* of each other, and do not appear to rationalize the observed reactivity.

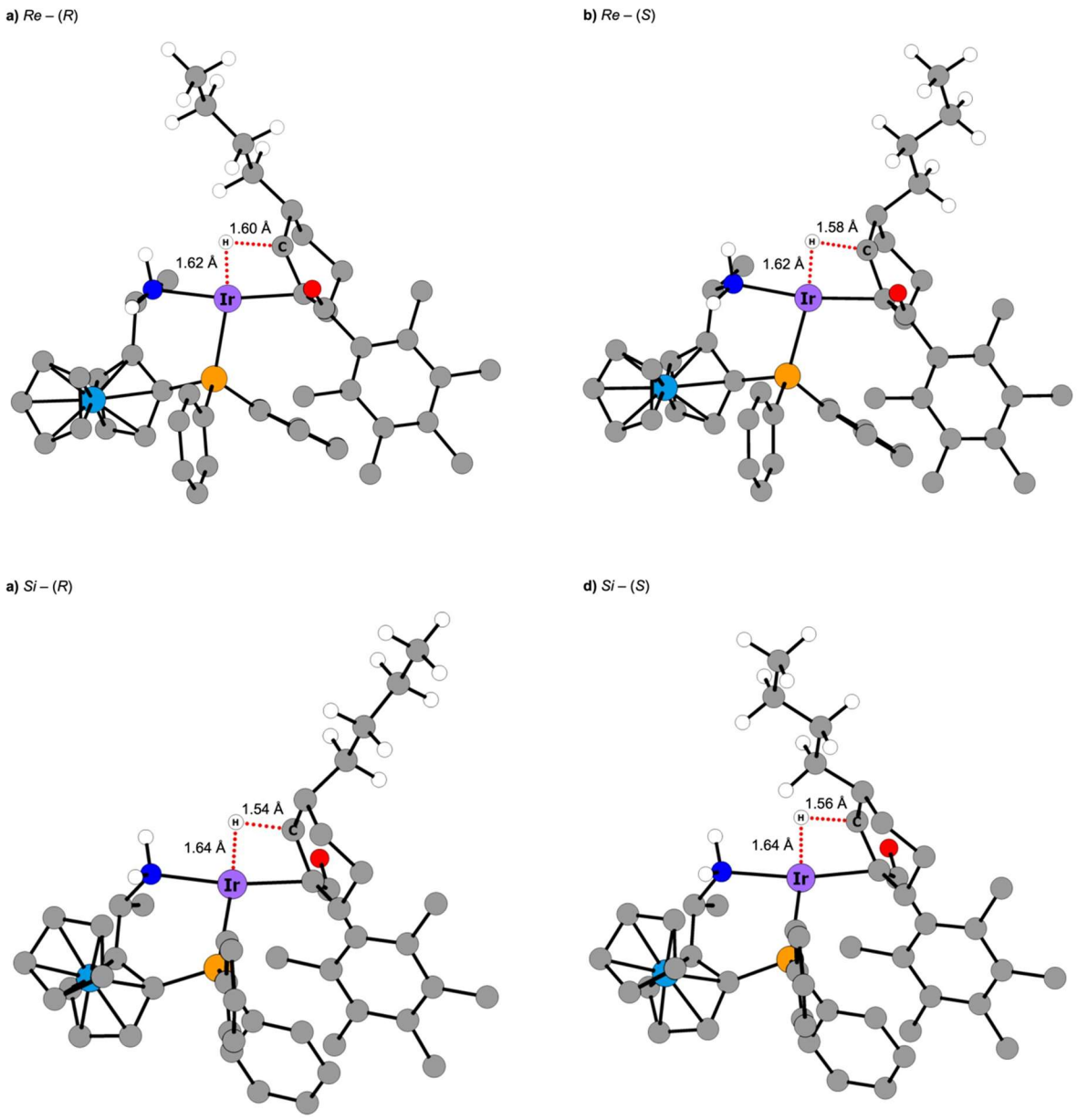


Figure SX4. Geometries of the hydride transfer TSs for R = Bu optimized at the ωB97X-D3BJ/def2-SVP level of theory: a) *Re* – (*R*), b) *Re* – (*S*), c) *Si* – (*R*), and d) *Si* – (*S*). The length of the Ir–H and H–C bonds being broken and formed, respectively, are indicated by numbers for each structure in Å. All H atoms attached to carbons, except for those belonging to the R = Bu group, have been removed for clarity. Ir, Fe, C, N, O, P and H are shown in purple, light blue, gray, dark blue, red, orange and white, respectively.

Table SX3. Barriers, geometric parameters and natural charges for the hydride migration TSs for R = Bu. Barriers are calculated at the ωB97X-D3BJ/def2-QZVP level of theory, geometric parameters at the ωB97X-D3BJ/def2-SVP level of theory, and natural charges at the ωB97X-D3BJ/def2-TZVP level of theory.

Configuration	$\Delta G^{\ddagger}$ [kcal mol^{-1}]	$r_{Ir–H}$ [Å]	$r_{H–C}$ [Å]	$r_{Ir–C}$ [Å]	$\angle_{Ir–H–C}$ [°]	q_{Ir} [e]	q_{H} [e]	q_{C} [e]
Re – (*R*)	2.5	1.62	1.60	2.14	83.3	-0.14	0.06	-0.24
Re – (*S*)	4.7	1.62	1.58	2.14	83.8	-0.14	0.07	-0.25
Si – (*R*)	6.5	1.64	1.54	2.17	85.8	-0.12	0.06	-0.24
Si – (*S*)	4.5	1.64	1.56	2.17	85.5	-0.12	0.05	-0.22

For the second step, namely the η^1-to-η^3 coordination-change TS, the *Re* – (*R*) TS, which has the highest barrier (8.2 kcal mol^{-1}), has the shortest Ir–C and Ir–O distances compared to the other three configurations (0.16 and 0.17 Å, respectively, relative to *Si* – (*S*)), implying a late TS with significant distortions from the reactant state. Also the *Re* – (*S*) TS has a relatively product-like TS, with a notably shorter Ir–O distance than the *Si*-face configurations (around 0.10 Å). On the other hand, the *Si* – (*R*) TS has the most reactant-like structure, but not the lowest barrier, exhibiting a short Ir–H distance. Also with respect to atomic charges, the highest-barrier *Re* – (*R*) configuration differs significantly from the other three configurations, displaying a much lower charge on the C and O that coordinate to Ir (around 0.1 and 0.05 *e*, respectively). These geometric parameters rationalize why the *Re*-face configurations have high-energy barriers that are disfavored, but not why *Si* – (*S*) has a lower barrier than *Si* – (*R*).

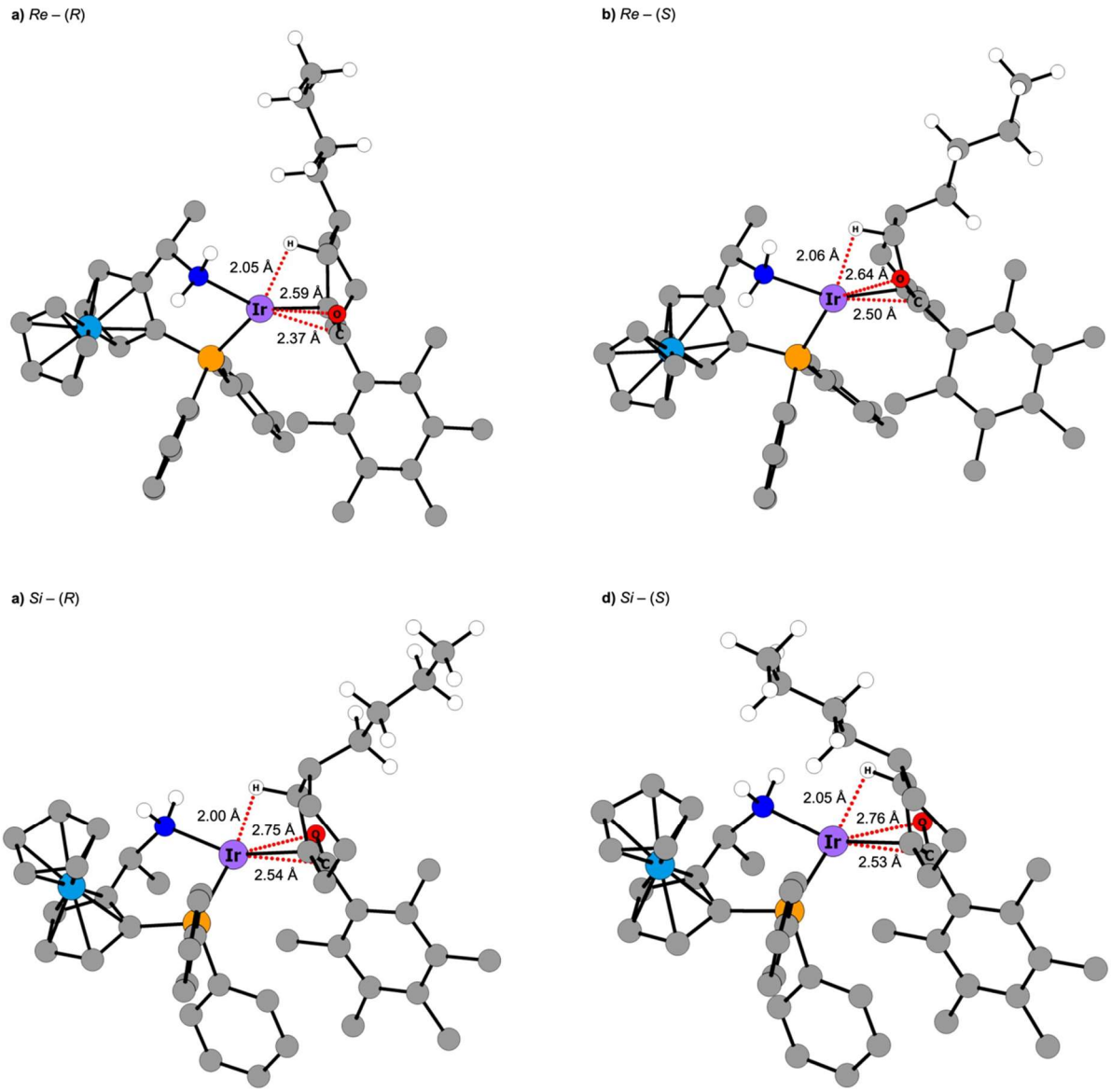


Figure SX5. Geometries of the coordination-change TSs for R = Bu optimized at the ωB97X-D3BJ/def2-SVP level of theory: a) *Re* – (*R*), b) *Re* – (*S*), c) *Si* – (*R*), and d) *Si* – (*S*). The length of the Ir–H bond being broken and the Ir–C and Ir–O bonds being formed are indicated by numbers for each structure in Å. All H atoms attached to carbons, except for those belonging to the R = Bu group, have been removed for clarity. Ir, Fe, C, N, O, P and H are shown in purple, light blue, gray, dark blue, red, orange and white, respectively.

Table SX4. Barriers, geometric parameters and natural charges for the η^1-to-η^3 coordination-change TSs for R = Bu. Barriers are calculated at the ωB97X-D3BJ/def2-QZVP level of theory, geometric parameters at the ωB97X-D3BJ/def2-SVP level of theory, and natural charges at the ωB97X-D3BJ/def2-TZVP level of theory.

Configuration	$\Delta G^{\ddagger}$ [kcal mol^{-1}]	r_{Ir-H} [Å]	r_{Ir-C} [Å]	r_{Ir-O} [Å]	q_{Ir} [e]	q_{H} [e]	q_{C} [e]	q_{O} [e]
Re – (*R*)	8.2	2.05	2.37	2.59	0.08	0.18	0.44	-0.78
Re – (*S*)	5.8	2.06	2.50	2.64	0.05	0.19	0.53	-0.73
Si – (*R*)	4.2	2.00	2.54	2.75	0.04	0.18	0.53	-0.73
Si – (*S*)	1.8	2.05	2.53	2.76	0.02	0.22	0.54	-0.73

The four hydride transfer TSs with R = Me are shown in Figure SX6, with geometric parameters and charges summarized in Table SX5. The situation with R = Me is similar to the R = Bu case for the hydride transfer. The corresponding coordination change TS structures with R = Me are shown in Figure SX7 and geometric parameters and charges are summarized in Table SX6. In this step, both the *Re* – (*R*) and *Re* – (*S*) TS structures are product-like (with r_{Ir-C} = 2.35 and 2.38 Å, respectively, and r_{Ir-O} = 2.59 and 2.59 Å, respectively) and high in energy ($\Delta G^{\ddagger}$ = 8.1 and 7.7 kcal mol^{-1}, respectively) as was previously observed for *Re* – (*R*) with R = Bu ($\Delta G^{\ddagger}$ = 8.2 kcal mol^{-1}, r_{Ir-C} = 2.37 Å and r_{Ir-O} = 2.59 Å). Overall, this destabilization of the *Re* – (*S*) coordination change TS results in lower selectivity for the (*S*) isomer product.

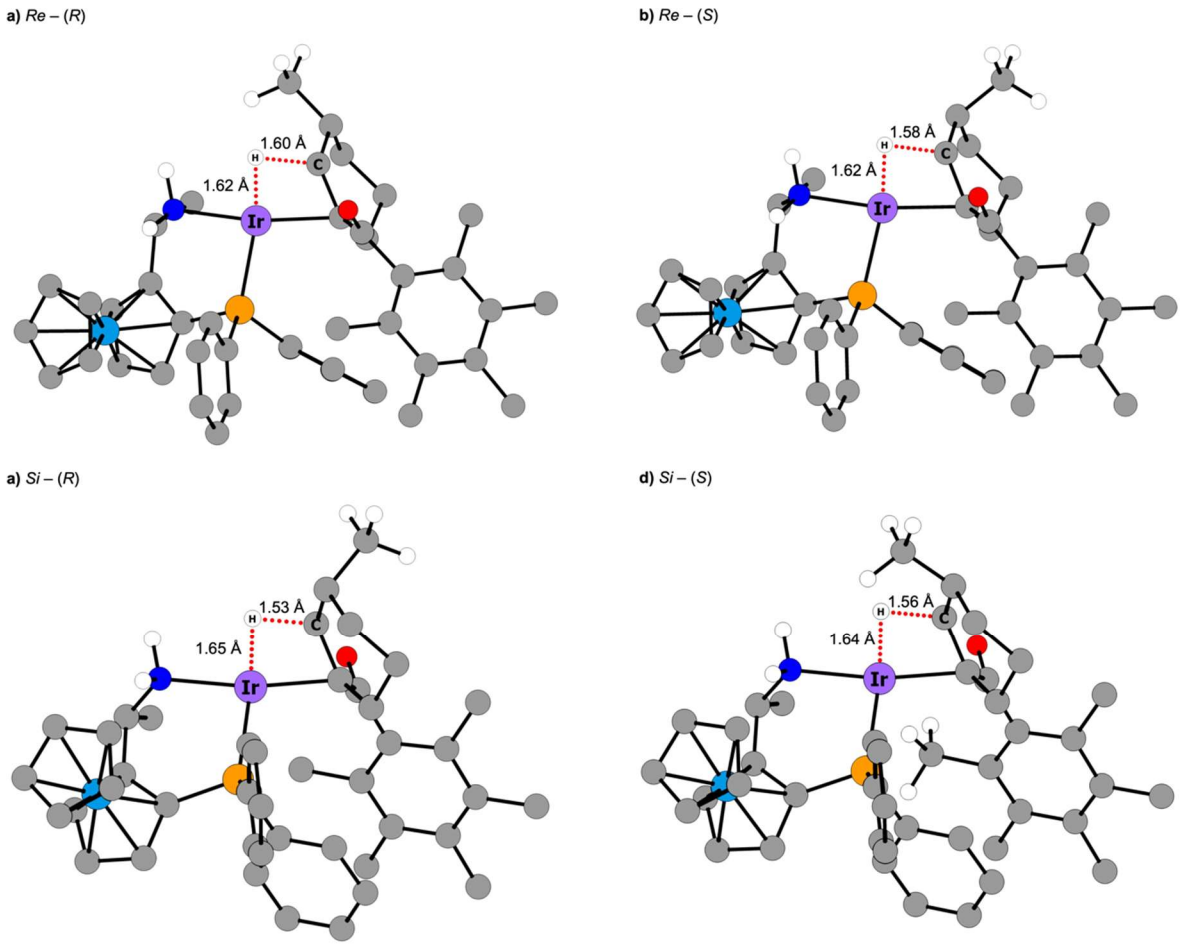


Figure SX6. Geometries of the hydride transfer TSs for R = Me optimized at the ωB97X-D3BJ/def2-SVP level of theory: a) *Re* – (*R*), b) *Re* – (*S*), c) *Si* – (*R*), and d) *Si* – (*S*). The length of the Ir–H and H–C bonds being broken and formed, respectively, are indicated by numbers for each structure in Å. All H atoms attached to carbons, except for those belonging to the R = Me group, have been removed for clarity. Ir, Fe, C, N, O, P and H are shown in purple, light blue, gray, dark blue, red, orange and white, respectively.

Table SX5. Barriers and geometric parameters for the hydride migration TSs for R = Me. Barriers are calculated at the ωB97X-D3BJ/def2-QZVP level of theory and geometric parameters at the ωB97X-D3BJ/def2-SVP level of theory.

Configuration	$\Delta G^{\ddagger}$ [kcal mol^{-1}]	$r_{Ir–H}$ [Å]	$r_{H–C}$ [Å]	$r_{Ir–C}$ [Å]	$\angle_{Ir–H–C}$ [°]
Re – (*R*)	2.3	1.62	1.60	2.14	83.3
Re – (*S*)	4.2	1.62	1.58	2.14	84.0
Si – (*R*)	5.6	1.65	1.53	2.17	86.0
Si – (*S*)	4.0	1.64	1.56	2.17	85.5

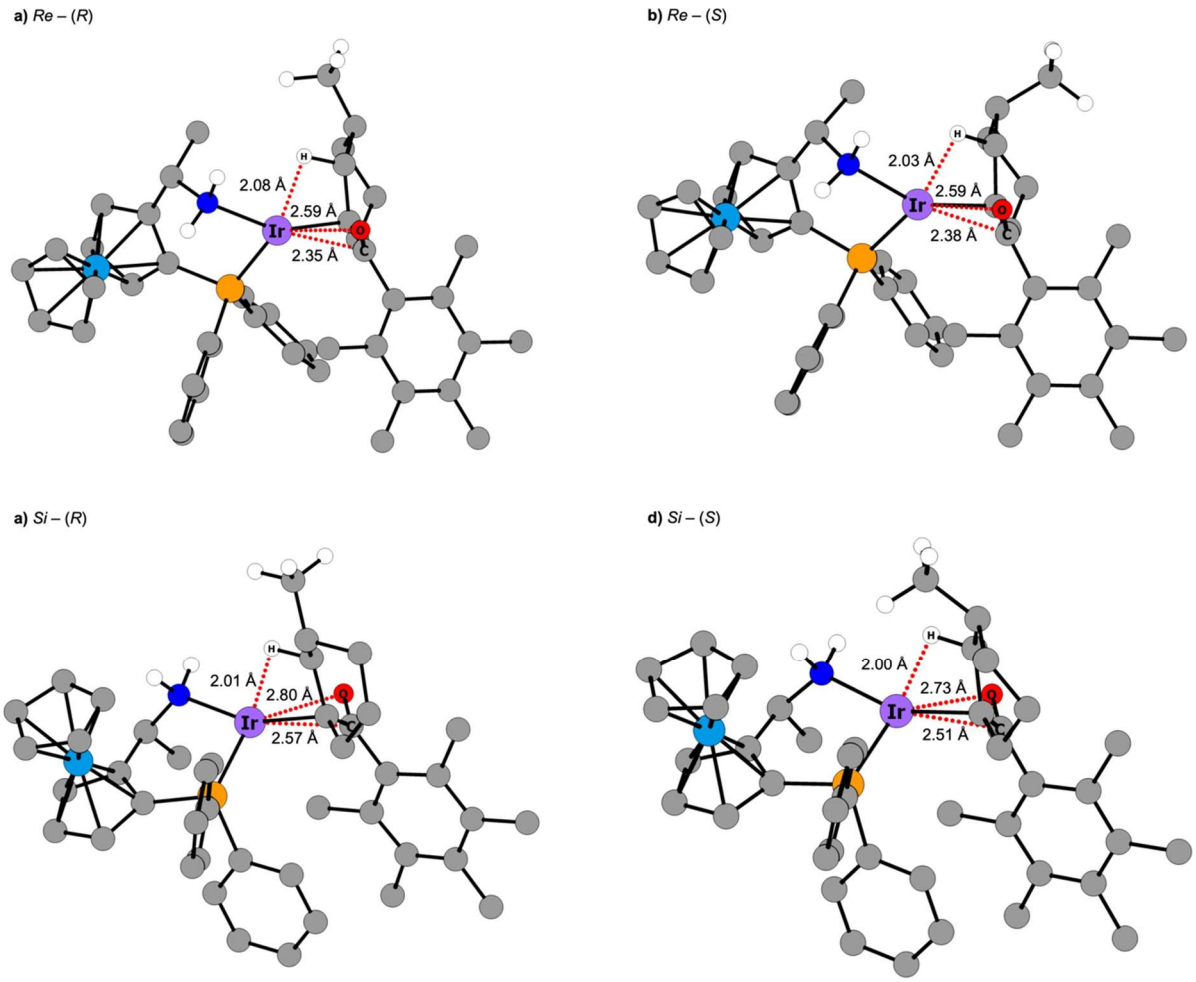


Figure SX7. Geometries of the coordination-change TSs for R = Me optimized at the ωB97X-D3BJ/def2-SVP level of theory: a) *Re* – (*R*), b) *Re* – (*S*), c) *Si* – (*R*), and d) *Si* – (*S*). The length of the Ir–H bond being broken and the Ir–C and Ir–O bonds being formed are indicated by numbers for each structure in Å. All H atoms attached to carbons, except for those belonging to the R = Me group, have been removed for clarity. Ir, Fe, C, N, O, P and H are shown in purple, light blue, gray, dark blue, red, orange and white, respectively.

Table SX6. Barriers and geometric parameters for the η^1-to-η^3 coordination-change TSs for R = Me. Barriers are calculated at the ωB97X-D3BJ/def2-QZVP level of theory and geometric parameters at the ωB97X-D3BJ/def2-SVP level of theory.

Configuration	$\Delta G^{\ddagger}$ [kcal mol^{-1}]	$r_{Ir–H}$ [Å]	$r_{Ir–C}$ [Å]	$r_{Ir–O}$ [Å]
Re – (*R*)	8.1	2.08	2.35	2.59
Re – (*S*)	7.7	2.03	2.38	2.59
Si – (*R*)	0.2	2.01	2.57	2.80
Si – (*S*)	1.3	2.00	2.51	2.73

Transition State Stabilization Interactions

NCI plots for the four hydride transfer TSs are shown in Figure SX8. The most stabilizing factor, seen in *Re* – (*R*) and *Si* – (*S*), is the interaction between the transferred hydride and the R = Bu group, whereas further interactions stabilizing the four TSs stem from π-interactions between the aromatic Ph rings of the PPh_2 moiety and the enone substrate. In the *Re*-face complexes *Re* – (*R*) and *Re* – (*R*), there are two such interactions; one in which both Ph groups interact with the Ph*, and another between one Ph and the cyclohexyl moiety. In the *Si*-face complexes *Si* – (*R*) and *Si* – (*S*), on the other hand, there is a staggered π-stacking between one of the Ph rings and the enone Ph*.

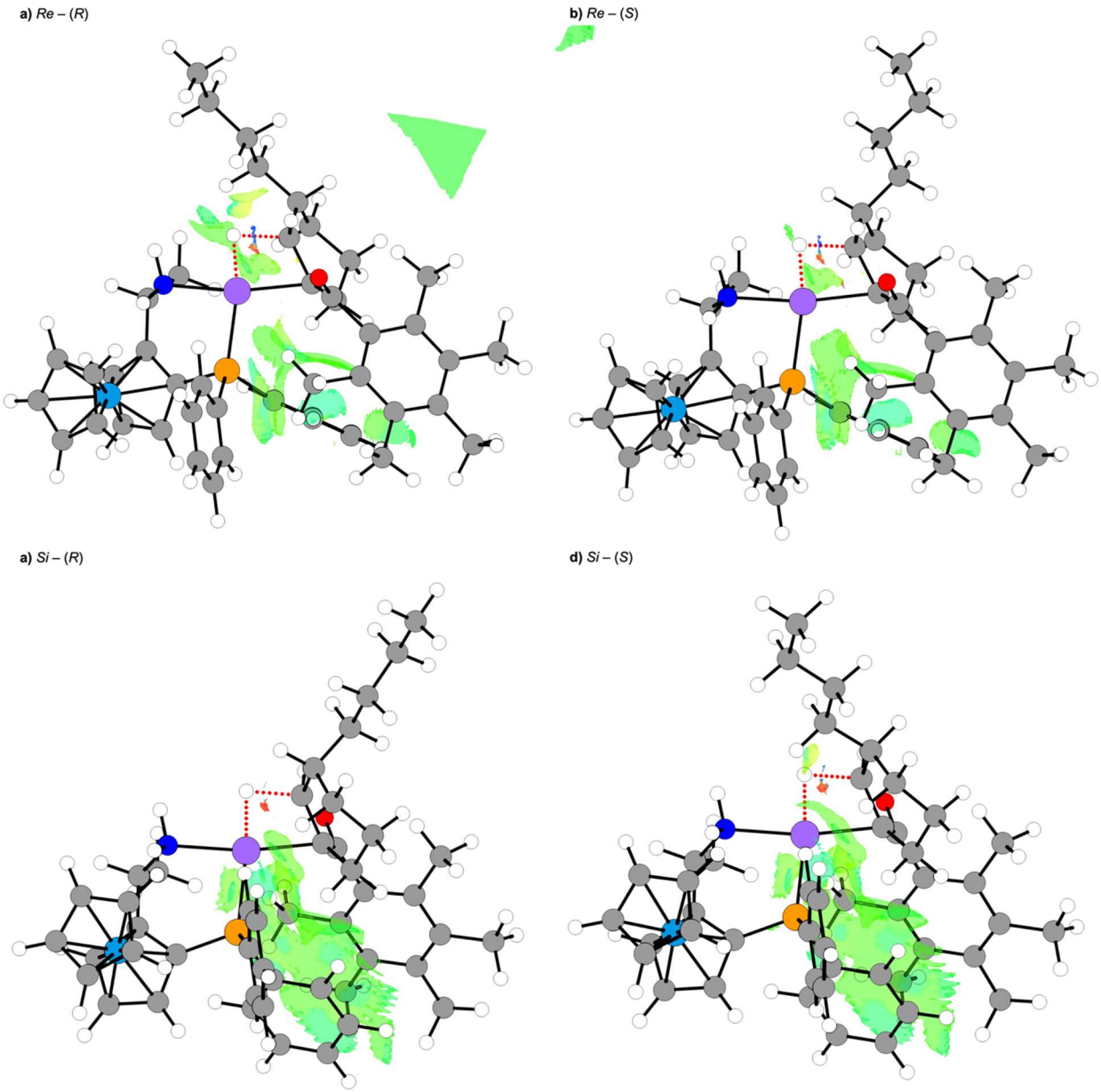


Figure SX8. NCI plots of the hydride transfer TSs for R = Bu optimized at the ωB97X-D3BJ/def2-SVP level of theory: a) *Re* – (*R*), b) *Re* – (*S*), c)– *Si* – (*R*), and d) *Si* – (*S*). Blue, green and red isosurface regions indicate strongly attractive, weakly attractive and repulsive interactions, respectively. Ir, Fe, C, N, O, P and H are shown in purple, light blue, gray, dark blue, red, orange and white, respectively.

NCI plots for the subsequent coordination-change TS are shown in Figure SX9. The two lowest-energy structures are the *Si*-face complexes *Si* – (*R*) and *Si* – (*S*), in which there is again a very clear staggered π-stacking between one of the aryl phosphine Ph rings and the Ph* moiety. In addition, the *Si* – (*S*) and *Re* –

(*R*) configurations with the Bu group oriented inwards, over the structure, possess NCIs between the butyl chain and the methyl moiety adjacent to the NH_2 group.

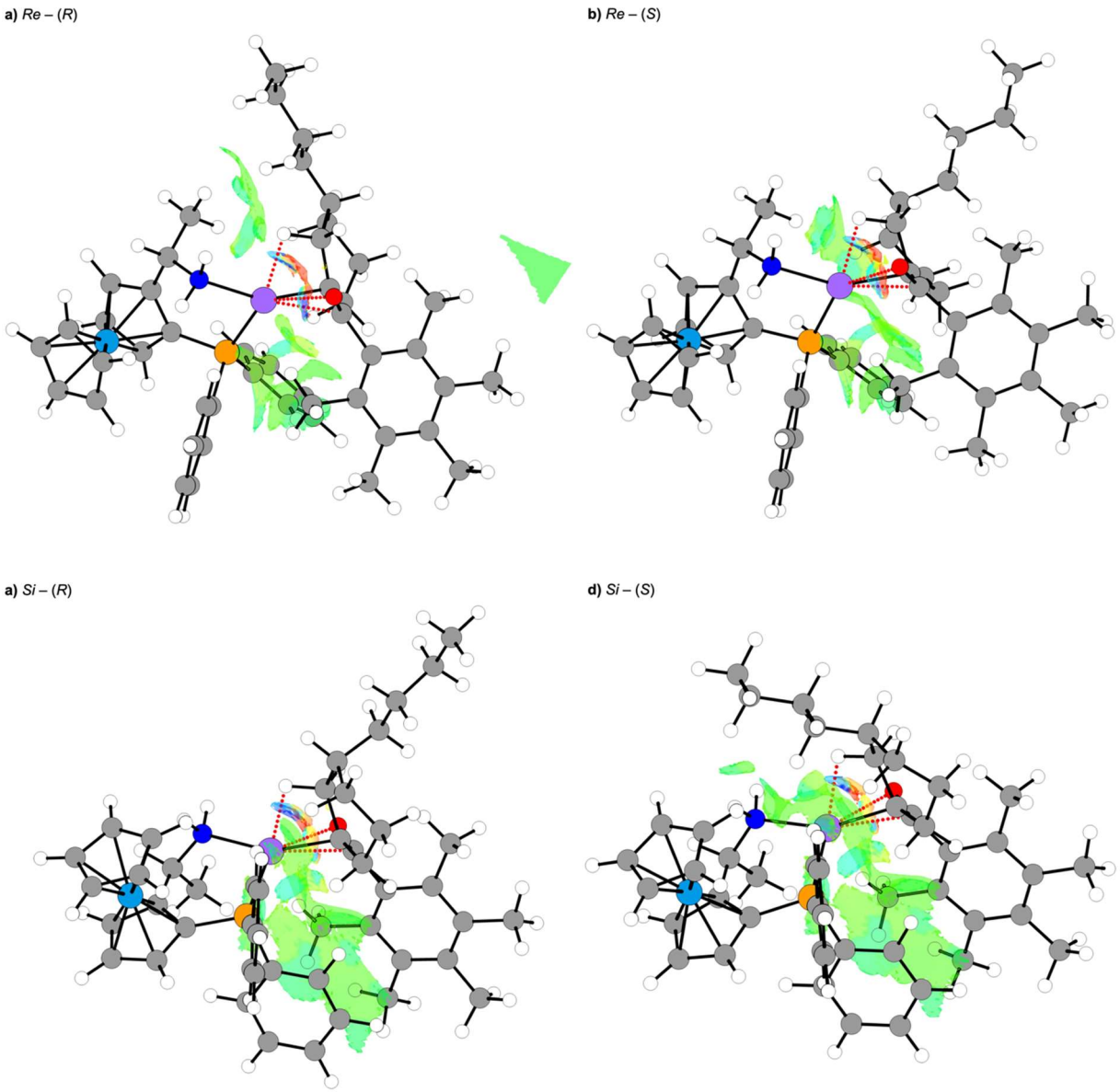


Figure SX9. NCI plots of the coordination-change TSs for R = Bu optimized at the ωB97X-D3BJ/def2-SVP level of theory: a) *Re* – (*R*), b) *Re* – (*S*), c) *Si* – (*R*), and d) *Si* – (*S*). Blue, green and red isosurface regions indicate strongly attractive, weakly attractive and repulsive interactions, respectively. Ir, Fe, C, N, O, P and H are shown in purple, light blue, gray, dark blue, red, orange and white, respectively.

To evaluate the energetic contributions of the stabilization attributable to the PPh_2 and the R = Bu groups, we conducted one experiment in which the PPh_2 group was replaced with PMe_2 to evaluate the impact of the π-interactions on the stabilization, and another in which R = Bu was replaced by H to evaluate how the

R group orientation affects the energy. Only the substituted groups were optimized to retain the original TS geometries. The results are summarized in Table SX7.

Table SX7. Relative energies ($\Delta E^{\ddagger}$) of the substituted TS structures and relative energies given relative to the lowest energy non-substituted TS structure ($\Delta\Delta E^{\ddagger}$) in kcal mol^{-1}.

Configuration	HAT				η^1-to-η^3			
	$PPh_2 \rightarrow PMe_2$		Bu → H		$PPh_2 \rightarrow PMe_2$		Bu → H	
	$\Delta E^{\ddagger}$	$\Delta\Delta E^{\ddagger}$	$\Delta E^{\ddagger}$	$\Delta\Delta E^{\ddagger}$	$\Delta E^{\ddagger}$	$\Delta\Delta E^{\ddagger}$	$\Delta E^{\ddagger}$	$\Delta\Delta E^{\ddagger}$
Re – (*R*)	1.1	0.0	0.0	0.0	5.4	-1.5	6.2	-0.7
Re – (*S*)	3.3	-0.1	0.2	-2.1	3.4	-1.8	3.6	-1.6
Si – (*R*)	1.5	-2.9	0.8	-2.4	2.6	-0.3	0.3	-2.5
Si – (*S*)	0.0	-2.4	0.5	-0.8	0.0	0.0	0.0	0.0

Replacing PPh_2 with PMe_2 in the hydride transfer TS results in a stabilization of the staggered π-stacking *Si* – (*R*) and *Si* – (*S*) of 2.4–2.9 kcal mol^{-1} relative to *Re* – (*R*), indicating that the stabilization partly involving both Ph rings is greater than the contribution of the parallel-displaced staggered π-stacking of *Si* – (*R*) and *Si* – (*S*). Removing the R = Bu group, on the other hand, shows a relative stabilization of 2.1–2.4 kcal mol^{-1} of the structures with the Bu group originally pointing outwards (*Re* – (*S*) and *Si* – (*R*)) compared to the *Re* – (*R*) structure with the Bu group pointing inwards, implying that the NCI interactions between R = Bu and the rest of the complex are important for stabilizing the TS.

For the following η^1-to-η^3 coordination-change TS, the substitution of PPh_2 with PMe_2 causes a relative stabilization of the non-π-stacking *Re* – (*R*) and *Si* – (*R*) structures of 1.5–1.8 kcal mol^{-1} compared to the π-stacking *Si* – (*S*). This stabilization implies a clear energetic preference for the observed π-stacking interactions. Similarly, the removal of the butyl group stabilizes *Re* – (*S*) and *Si* – (*R*) by 1.6–2.5 kcal mol^{-1} relative to *Si* – (*S*), highlighting the stabilization contributions of the Bu group interacting with the Ir-complex.

To obtain further insights into the donor–acceptor interactions involved in stabilizing the TSs, we performed NBO calculations, including second order perturbation analysis. However, this analysis did not give any

indications about which particular interactions are responsible for the stabilizations, likely caused by the small energetic differences between the different configurations.

Calculated Energies

Calculated energies for the structures along the hydride transfer reaction with R = Me in Tables SX8–SX11, and with R = Bu in Tables SX12–SX15. *G*, *H* and *E* refer to Gibbs' free energy, enthalpy and electronic energy calculated at the ωB97X-D3BJ/def2-SVP level of theory, while *E'* is the electronic energy calculated at the ωB97X-D3BJ/def2-QZVP level. *G'* and *H'* are estimated by including the ωB97X-D3BJ/def2-QZVP electronic energy as

$$G' = G - E + E', \tag{2}$$

and

$$H' = H - E + E', \tag{3}$$

respectively.

Table SX8. Energies of the *Re* – (*R*) structures for R = Me in Hartree.

Structure	*G* [au]	*H* [au]	*E* [au]	*E'* [au]	*G'* [au]	*H'* [au]
Reactant complex	-3507.5400	-3507.3614	-3508.2827	-3510.6196	-3509.8769	-3509.6983
HAT TS	-3507.5368	-3507.3593	-3508.2785	-3510.6151	-3509.8734	-3509.6959
Intermediate	-3507.5432	-3507.3650	-3508.2879	-3510.6252	-3509.8805	-3509.7023
η^1-to-η^3 TS	-3507.5263	-3507.3498	-3508.2714	-3510.6092	-3509.8641	-3509.6875
Product complex	-3507.5676	-3507.3887	-3508.3123	-3510.6490	-3509.9043	-3509.7254

Table SX9. Energies of the *Re* – (*S*) structures for R = Me in Hartree.

Structure	*G* [au]	*H* [au]	*E* [au]	*E'* [au]	*G'* [au]	*H'* [au]
Reactant complex	-3507.5365	-3507.3583	-3508.2799	-3510.6163	-3509.8729	-3509.6947
HAT TS	-3507.5335	-3507.3561	-3508.2757	-3510.6125	-3509.8703	-3509.6929
Intermediate	-3507.5397	-3507.3618	-3508.2849	-3510.6221	-3509.8769	-3509.6989
η^1-to-η^3 TS	-3507.5268	-3507.3491	-3508.2707	-3510.6086	-3509.8647	-3509.6870
Product complex	-3507.5571	-3507.3788	-3508.3026	-3510.6383	-3509.8928	-3509.7144

Table SX10. Energies of the *Si* – (*R*) structures for R = Me in Hartree.

Structure	*G* [au]	*H* [au]	*E* [au]	*E'* [au]	*G'* [au]	*H'* [au]
Reactant complex	-3507.5399	-3507.3631	-3508.2851	-3510.6206	-3509.8754	-3509.6986
HAT TS	-3507.5328	-3507.3566	-3508.2762	-3510.6116	-3509.8681	-3509.6920
Intermediate	-3507.5414	-3507.3635	-3508.2862	-3510.6220	-3509.8772	-3509.6993
η^1-to-η^3 TS	-3507.5402	-3507.3634	-3508.2849	-3510.6215	-3509.8767	-3509.6999
Product complex	-3507.5669	-3507.3889	-3508.3127	-3510.6494	-3509.9036	-3509.7256

Table SX11. Energies of the *Si* – (*S*) structures for R = Me in Hartree.

Structure	*G* [au]	*H* [au]	*E* [au]	*E'* [au]	*G'* [au]	*H'* [au]
Reactant complex	-3507.5421	-3507.3651	-3508.2869	-3510.6218	-3509.8770	-3509.7000
HAT TS	-3507.5355	-3507.3594	-3508.2788	-3510.6140	-3509.8706	-3509.6945
Intermediate	-3507.5416	-3507.3640	-3508.2869	-3510.6228	-3509.8775	-3509.6999
η^1-to-η^3 TS	-3507.5387	-3507.3625	-3508.2842	-3510.6205	-3509.8750	-3509.6988
Product complex	-3507.5723	-3507.3946	-3508.3183	-3510.6550	-3509.9090	-3509.7313

Table SX12. Energies of the *Re* – (*R*) structures for R = Bu in Hartree.

Structure	*G* [au]	*H* [au]	*E* [au]	*E'* [au]	*G'* [au]	*H'* [au]
Reactant complex	-3625.3941	-3625.2024	-3626.2159	-3628.6838	-3627.8620	-3627.6703
HAT TS	-3625.3905	-3625.2002	-3626.2118	-3628.6793	-3627.8581	-3627.6677
Intermediate	-3625.3967	-3625.2057	-3626.2209	-3628.6890	-3627.8648	-3627.6738
η^1-to-η^3 TS	-3625.3801	-3625.1908	-3626.2048	-3628.6736	-3627.8490	-3627.6596
Product complex	-3625.4217	-3625.2310	-3626.2470	-3628.7142	-3627.8889	-3627.6982

Table SX13. Energies of the *Re* – (*S*) structures for R = Bu in Hartree.

Structure	*G* [au]	*H* [au]	*E* [au]	*E'* [au]	*G'* [au]	*H'* [au]
Reactant complex	-3625.3895	-3625.1981	-3626.2120	-3628.6793	-3627.8569	-3627.6654
HAT TS	-3625.3867	-3625.1960	-3626.2079	-3628.6757	-3627.8545	-3627.6638
Intermediate	-3625.3939	-3625.2038	-3626.2196	-3628.6869	-3627.8612	-3627.6711
η^1-to-η^3 TS	-3625.3846	-3625.1943	-3626.2082	-3628.6763	-3627.8527	-3627.6624
Product complex	-3625.4138	-3625.2238	-3626.2402	-3628.7070	-3627.8806	-3627.6906

Table SX14. Energies of the *Si* – (*R*) structures for R = Bu in Hartree.

Structure	*G* [au]	*H* [au]	*E* [au]	*E'* [au]	*G'* [au]	*H'* [au]
Reactant complex	-3625.3936	-3625.2026	-3626.2166	-3628.6835	-3627.8604	-3627.6695
HAT TS	-3625.3853	-3625.1959	-3626.2078	-3628.6742	-3627.8517	-3627.6623

Intermediate	-3625.3910	-3625.2005	-3626.2158	-3628.6828	-3627.8580	-3627.6675
η^1-to-η^3 TS	-3625.3880	-3625.1988	-3626.2129	-3628.6801	-3627.8552	-3627.6660
Product complex	-3625.4145	-3625.2242	-3626.2405	-3628.7080	-3627.8820	-3627.6917

Table SX15. Energies of the *Si* – (*S*) structures for R = Bu in Hartree.

Structure	*G* [au]	*H* [au]	*E* [au]	*E'* [au]	*G'* [au]	*H'* [au]
Reactant complex	-3625.3960	-3625.2054	-3626.2195	-3628.6855	-3627.8620	-3627.6714
HAT TS	-3625.3886	-3625.1992	-3626.2110	-3628.6773	-3627.8548	-3627.6654
Intermediate	-3625.3947	-3625.2045	-3626.2197	-3628.6864	-3627.8614	-3627.6712
η^1-to-η^3 TS	-3625.3924	-3625.2037	-3626.2179	-3628.6846	-3627.8592	-3627.6704
Product complex	-3625.4120	-3625.2237	-3626.2405	-3628.7064	-3627.8779	-3627.6896

References

[1] F. Neese, F. Wennmohs, U. Becker, C. Riplinger, *J. Chem. Phys.* **2020**, *152*, 224108.
[2] J. G. Brandenburg, C. Bannwarth, A. Hansen, S. Grimme, *The Journal of Chemical Physics* **2018**, *148*, 064104.
[3] J.-D. Chai, M. Head-Gordon, *The Journal of Chemical Physics* **2008**, *128*, 084106.
[4] A. Najibi, L. Goerigk, *J. Chem. Theory Comput.* **2018**, *14*, 5725–5738.
[5] F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297.
[6] K. Eichkorn, O. Treutler, H. Öhm, M. Häser, R. Ahlrichs, *Chemical Physics Letters* **1995**, *240*, 283–290.
[7] F. Neese, *J Comput Chem* **2003**, *24*, 1740–1747.
[8] F. Weigend, *Phys. Chem. Chem. Phys.* **2006**, *8*, 1057.
[9] F. Neese, F. Wennmohs, A. Hansen, U. Becker, *Chemical Physics* **2009**, *356*, 98–109.
[10] V. Barone, M. Cossi, *J. Phys. Chem. A* **1998**, *102*, 1995–2001.
[11] P. Winget, D. M. Dolney, D. J. Giesen, C. J. Cramer, D. G. Truhlar, **2021**, DOI https://comp.chem.umn.edu/solvation/mnsddb.pdf.
[12] K. Ishida, K. Morokuma, A. Komornicki, *The Journal of Chemical Physics* **1977**, *66*, 2153–2156.
[13] T. Young, **2020**, DOI 10.5281/ZENODO.4005686.
[14] S. Grimme, *Chemistry A European J* **2012**, *18*, 9955–9964.
[15] E. D. Glendening, C. R. Landis, F. Weinhold, *J Comput Chem* **2019**, *40*, 2234–2241.
[16] R. A. Boto, F. Peccati, R. Laplaza, C. Quan, A. Carbone, J.-P. Piquemal, Y. Maday, J. Contreras-García, *J. Chem. Theory Comput.* **2020**, *16*, 4150–4158.
[17] M. Álvarez-Moreno, C. de Graaf, N. López, F. Maseras, J. M. Poblet, C. Bo, *J. Chem. Inf. Model.* **2015**, *55*, 95–103.