Supporting Information for:

Expedient Preparation of Active Pharmaceutical Ingredient Ketamine under Sustainable Continuous Flow Conditions

Victor-Emmanuel Kassin,[a,†] Romaric Gérardy,[a,†] Thomas Toupy,[a] Diégo Collin,[a] Elena Salvadeo,[a,b] François Toussaint,[a] Kristof Van Hecke[c] and Jean-Christophe M. Monbaliu[a,*]

[a] *Center for Integrated Technology and Organic Synthesis, Research Unit MolSys, University of Liège, B-4000 Liège (Sart Tilman), Belgium*
[b] *Alysophil SAS, 2000 Route des Lucioles Starter Business Center – CS 70337 Les Algorithmes – Bât Thalès, 06410 Biot - Sophia Antipolis, France*
[c] *XStruct, Department of Chemistry, Ghent University, Krijgslaan 281-S3, B-9000 Ghent, Belgium*

Table of Contents

1. Continuous flow setups 4
1.1 Microfluidic setups and parts 4
1.1.1 Pumps 4
1.1.2 Mass flow controller 4
1.1.3 SS coil reactors 4
1.1.4 SS packed-bed reactor 4
1.1.5 PEEK tubing 4
1.1.6 PFA tubing and coils 4
1.1.7 Connectors, ferrules and mixers 4
1.1.8 Check-valves 4
1.1.9 Back-pressure regulators 5
1.1.10 Thermoregulatory devices 5
1.2 Mesofluidic setup 5
1.2.1 Pumps 5
1.2.2 Mass flow controller 5
1.2.3 Mesofluidic reactor 5
1.2.4 Thermoregulatory devices 5
1.2.5 Back-pressure regulators 5
1.3 Part numbers & vendors 6
1.4 Detailed continuous flow setups 8

1.4.1 Hydroxylation of ketone 2 (homogeneous) 8
1.4.2 Hydroxylation of ketone 2 (heterogeneous) 9
1.4.3 Large scale hydroxylation of ketone 2 (homogeneous) 10
1.4.4 High temperature imination of hydroxyketone 7 11
1.4.5 Trialkyl borate-promoted imination of hydroxyketone 7 12
1.4.6 Thermolysis of iminol 4a (homogeneous conditions) 13
1.4.7 Thermolysis of iminol 4a (heterogeneous conditions) 14
1.4.8 Concatenated hydroxylation and imination steps (homogeneous conditions) 15
1.4.9 Concatenated process toward (±)-1a and analogs (±)-1b,c 16
2. Additional experimental details 17
2.1 Chemicals 17
2.2 Additional experimental data 19
2.2.1 Batch procedure for the synthesis of (2-chlorophenyl)cyclopentyl ketone (2) 19
2.2.2 Optimization of the hydroxylation of ketone 2 under homogeneous conditions 19
2.2.3 Optimization of the hydroxylation of ketone 2 under heterogeneous conditions 31
2.2.4 Imination of (±)-(2-chlorophenyl)(1-hydroxycyclopentyl)methanone (7) under continuous flow conditions without additive 33
2.2.5 Batch procedure for the synthesis of α-iminol 4a 34
2.2.6 Concatenated two-step continuous flow process toward α-iminol 4a (microfluidic setup) 35
2.2.7 Preliminary optimization for the thermal rearrangement of α-iminol 4a under microwave conditions 36
2.2.8 Preliminary optimization for the thermal rearrangement of α-iminol 4a under continuous flow homogeneous conditions 37
2.2.9 Preliminary optimization for the thermal rearrangement of α-iminol 4a under continuous flow heterogeneous conditions 38
2.2.10 Concatenated three-step continuous flow process toward (±)-ketamine (1a) (microfluidic setup) 39
2.3 Characterization of compounds 40
2.4 Structural identification of *N*-(2-chlorobenzylidene)methanamine (8) 42
2.5 LC analysis of key intermediates 44
2.5.1 Analytical Method 44
2.5.2 Copies of LC traces 45
2.6 Copies of ^{1}H and ^{13}C NMR spectra 48
2.7 Copies of IR spectra for compounds 4c and (±)-1c 57
2.8 Molecular structure by single crystal X-ray diffraction analysis of compounds iso-7, 4a and 1a 58

2.8.1 General information 58
2.8.2 Crystal data for compounds iso-7, 4a and 1a 58
3 Computations 62
3.1 α-Ketol rearrangement on hydroxy cyclopentylphenylketones mod-7 and 7 62
3.2 α-Iminol rearrangement on α-hydroxy cyclopentylphenylimines 4¸4a, 4b and 4c 66
3.3 α-Iminol rearrangement on α-hydroxy cyclopentylphenylimine 4a in the presence of a Lewis acid 74
3.4 α-Aminoketone rearrangement on α-amino cyclopentylphenylketones 1 and 1a 76
3.5 α-Iminol rearrangement of α-hydroxy cyclopentylphenylimines iso-1 and iso-1a 80
3.6 Conformational study on compound iso-7 84
4 References 86

1. Continuous flow setups

1.1 Microfluidic setups and parts

All microfluidic setups were assembled with commercially available parts.

1.1.1 Pumps

ThalesNano microHPLC® pumps (wetted parts: SS 316, ruby and sapphire) or Chemyx Fusion 6000® High Force syringe pumps equipped with stainless steel syringes (6 ou 20 mL) with Dupont™ Kalrez® Spectrum™ AS-568 O-rings (0.549 x 0.103”) were utilized to handle the liquid feeds.

1.1.2 Mass flow controller

The gas feed (oxygen or air) was handled with a Bronkhorst EL FLOW Prestige mass flow controller.

1.1.3 SS coil reactors

SS coil reactors were constructed with deburred-end, steam-cleaned and acid-passivated 316 SS tubing (1.58 mm outer diameter, 500 µm internal diameter) of defined internal volumes.

1.1.4 SS packed-bed reactor

Packed-bed reactors were assembled from SS columns (12.5 cm × 7 mm o.d. × 4 mm i.d. or 10 cm × 13 mm o.d. × 9 mm i.d.) with Valco connectors.

1.1.5 PEEK tubing

Feed lines were constructed from PEEK tubing (green striped, 1.58 mm outer diameter, 750 µm internal diameter).

1.1.6 PFA tubing and coils

PFA coil reactors and collection lines were constructed from PFA tubing (high purity PFA; 1.58 mm outer diameter, 750 µm internal diameter).

1.1.7 Connectors, ferrules and mixers

Sections of the reactor that were not subjected to high temperatures were equipped with Super Flangeless nuts and ferrules or coned PEEK fittings, and micromixers. Sections of the reactor that were subjected to high temperatures were equipped Valco SS fittings, ferrules and unions. Connectors, ferrules and unions were purchased from IDEX/Upchurch (details in Table S1).

1.1.8 Check-valves

The check-valves inserted between the pumps and the reactors were purchased from IDEX/Upchurch Scientific (PEEK or SS check-valve holder).

1.1.9 Back-pressure regulators

Spring loaded BPRs were purchased from IDEX/Upchurch Scientific (PEEK or SS check-valve holder). Dome-type BPRs were purchased from Zaiput Flow Technologies. The dome-type BPR was connected to a compressed gas cylinder (nitrogen) to set the working pressure.

1.1.10 Thermoregulatory devices

PFA coils, SS coils and packed-bed reactors operated at temperatures up to 180 °C were thermoregulated in oil baths (Heidolph™ MR Hei-Tec® equipped with Pt-1000 temperature sensors). SS coils and packed-bed reactors operated at temperatures above 180 °C were thermoregulated in a modified GC oven.

1.2 Mesofluidic setup

1.2.1 Pumps

The liquid feed was handled with a Corning dosing line (FUJI Technologies™ pumps).

1.2.2 Mass flow controller

The gas feed (oxygen) was handled with a Bronkhorst EL FLOW Select mass flow controller.

1.2.3 Mesofluidic reactor

The mesofluidic setup utilized for the hydroxylation step was manufactured by Corning SAS (Corning® Advanced-Flow™ SiC G1 reactor) and equipped with 6 fluidic modules connected in series (60 mL total internal volume). In some experiments, a residence time unit (PFA loop, 1/8” o.d., 40 mL internal volume) was added downstream.

1.2.4 Thermoregulatory devices

The reactor was maintained at reaction temperature with a LAUDA Integral XT 280 thermostat (THERM 180 thermofluid).

1.2.5 Back-pressure regulators

A dome-type BPR from Zaiput Flow Technologies connected to a compressed gas cylinder (nitrogen) was utilized to set the working pressure.

1.3 Part numbers & vendors

Standard fluidic elements and connectors were purchased from IDEX/Upchurch Scientific, Valco Instruments Co. Inc and Zaiput Flow Technologies (Table S1).

Table S1. Connectors, ferrules and unions

Item	Details	Vendor	Reference
Connectors	One-Piece Fingertight, PEEK, 10-32 Coned, for 1/16” OD	IDEX/ Upchurch Scientific	F-120X
	Super Flangeless Nuts, natural PEEK 1/4-28 thread for 1/16” OD tubing	IDEX/ Upchurch Scientific	P-255X
	Super Flangeless Ferrule Tefzel (ETFE) and SS ring 1/4-28 thread for 1/16” OD tubing	IDEX/ Upchurch Scientific	P-259X
	SS Nut, standard, for 1/16” OD tubing	VICI (Valco Ins. Co. Inc.)	ZN1-10
	SS ferrule, 303, for 1/16” OD tubing	VICI (Valco Ins. Co. Inc.)	ZF1-10
Unions	Natural polypropylene standard low pressure union 1/4-28	IDEX/ Upchurch Scientific	P-620
	SS ZDV union Valco type for 1/16” OD, tubing	IDEX/ Upchurch Scientific	U-322
Mixers	T-mixer, natural PEEK 1/4-28 thread for 1/16" o.d. tubing, 0.02" through hole	IDEX/ Upchurch Scientific	P-712
	Cross Assembly, natural PEEK, 1/4-28 thread for 1/16" o.d. tubing, 0.02" through hole	IDEX/ Upchurch Scientific	P-722
Check-valve	Check-valve inline cartridge 1.5 psi	IDEX/ Upchurch Scientific	CV-3001
Spring-loaded BPR	BPR cartridge with gold coating (various set points)	IDEX/ Upchurch Scientific	P-763
Cartridge	BPR and check-valve cartridge holder, SS	IDEX/	U-469

holder		Upchurch Scientific	
Dome-type BPR	Dome-type BPR, metal-free, with adjustable set point	Zaiput Flow Techn.	BPR-10
Tubing	316 SS tubing (1.58 mm outer diameter, 500 µm internal diameter)	VICI (Valco Ins. Co. Inc.)	TSS120
	PEEK tubing (green striped, 1.58 mm outer diameter, 750 µm internal diameter).	VICI (Valco Ins. Co. Inc.)	JR-T-6003-M3
	High-purity PFA tubing, 1.58 mm outer diameter, 750 µm internal diameter	VICI (Valco Ins. Co. Inc.)	JR-T-4002-M25

1.4 Detailed continuous flow setups

1.4.1 Hydroxylation of ketone **2** (homogeneous)

See manuscript for experimental details (Figure 3a, Table 1).

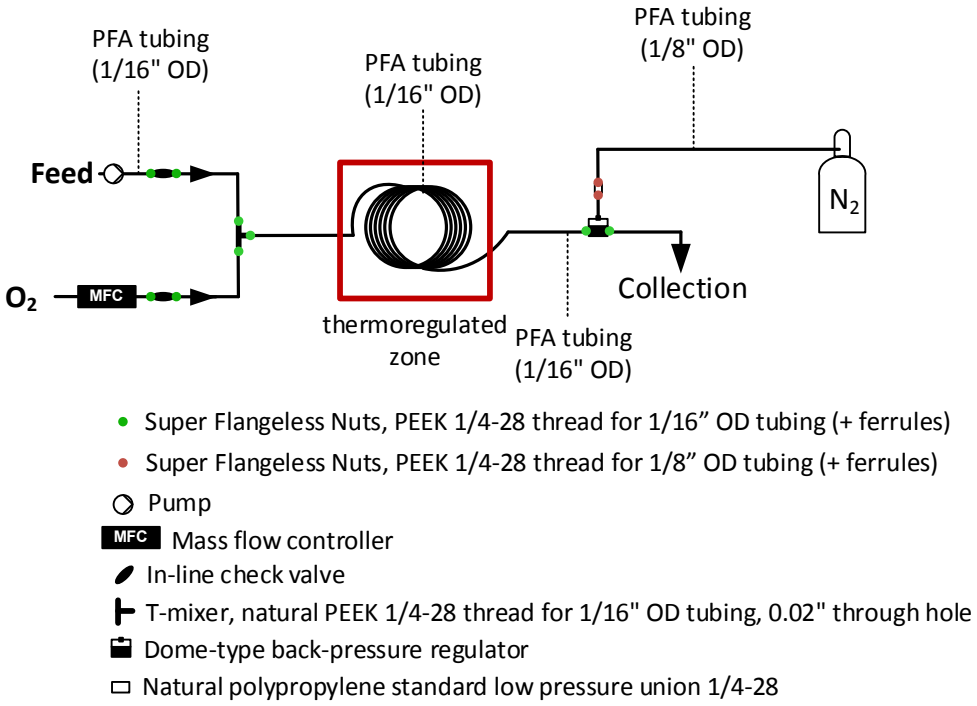


Figure S1. Detailed setup for the continuous flow hydroxylation of ketone **2** (homogeneous conditions)

1.4.2 Hydroxylation of ketone **2** (heterogeneous)

See manuscript for experimental details (Figure 4b, Table 2).

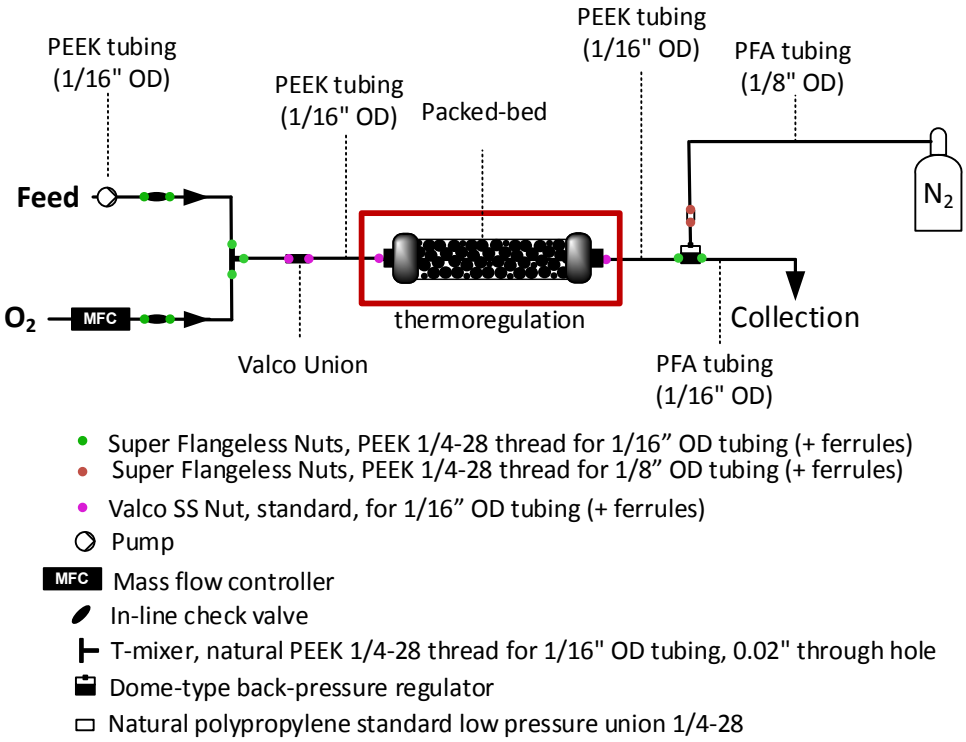


Figure S2. Detailed setup for the continuous flow hydroxylation of ketone **2** (heterogeneous conditions)

1.4.3 Large scale hydroxylation of ketone **2** (homogeneous)

See manuscript for experimental details (Figure 6).

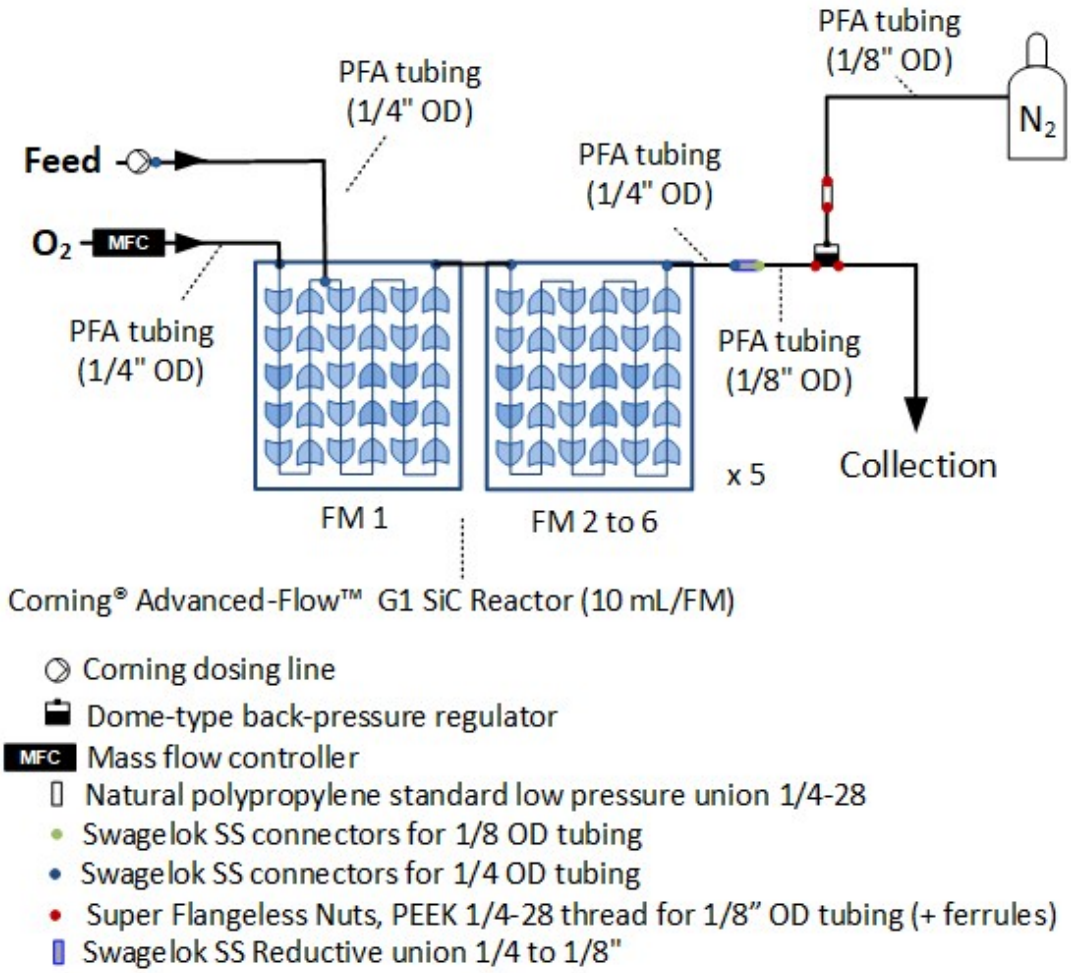


Figure S3. Detailed setup for the large-scale continuous flow hydroxylation of ketone **2** (homogeneous conditions)

1.4.4 High temperature imination of hydroxyketone **7**

See manuscript for experimental details (Figure 7a) and Supporting Information (Figure S14). The thermoregulated zone includes a cooling loop downstream the reaction loop (not shown).

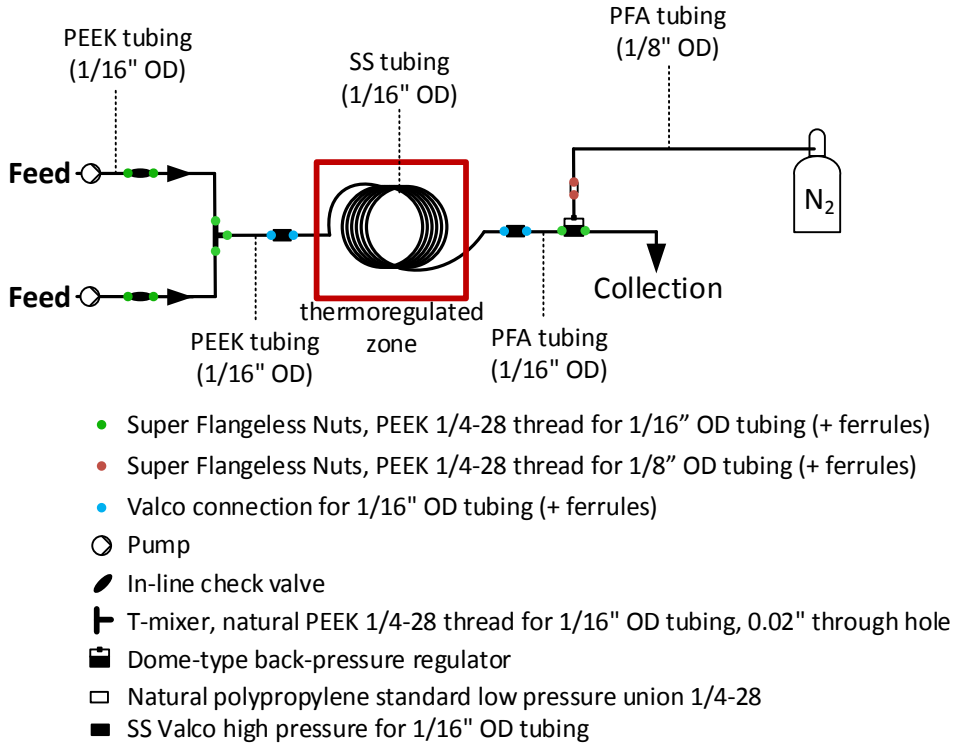


Figure S4. Detailed setup for the high temperature imination of hydroxyketone **7**

1.4.5 Trialkyl borate-promoted imination of hydroxyketone **7**

See manuscript for experimental details (Figure 7b, Table 3).

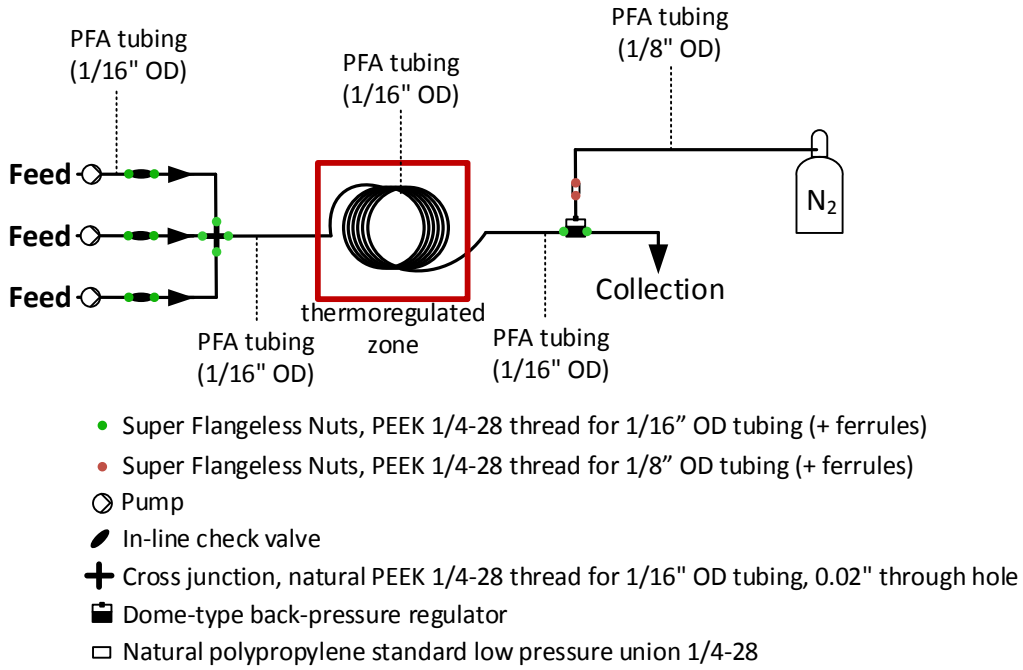
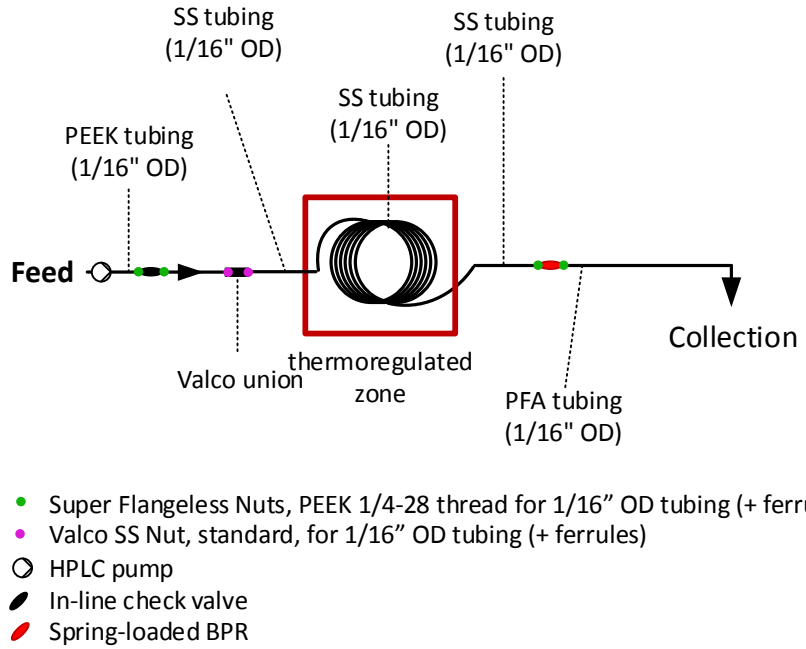


Figure S5. Detailed setup for the trialkyl borate-promoted imination of hydroxyketone **7**

1.4.6 Thermolysis of iminol **4a** (homogeneous conditions)

See manuscript for experimental details (Figure 9a, Tables 4,5). The thermoregulated zone includes preheating and cooling loops up- and downstream the reaction loop, respectively (not shown).

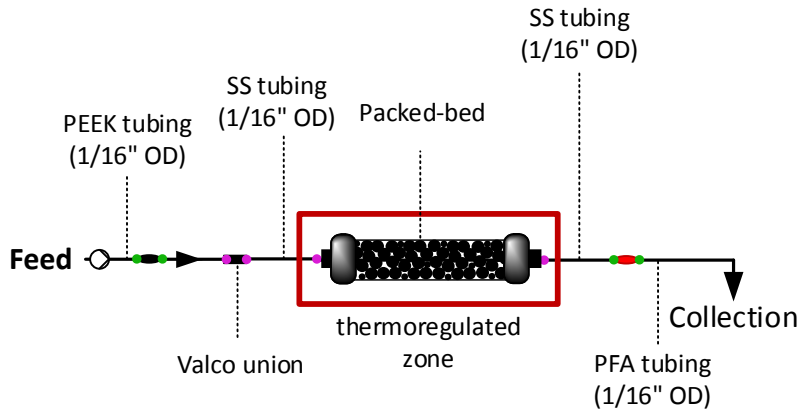


- Super Flangeless Nuts, PEEK 1/4-28 thread for 1/16” OD tubing (+ ferrules)
- Valco SS Nut, standard, for 1/16” OD tubing (+ ferrules)
- HPLC pump
- In-line check valve
- Spring-loaded BPR

Figure S6. Detailed setup for the continuous flow thermolysis of iminol **4a** (homogeneous conditions)

1.4.7 Thermolysis of iminol **4a** (heterogeneous conditions)

See manuscript for experimental details (Figure 9b, Table 6). The thermoregulated zone includes preheating and cooling loops up- and downstream the packed-bed reactor, respectively (not shown).

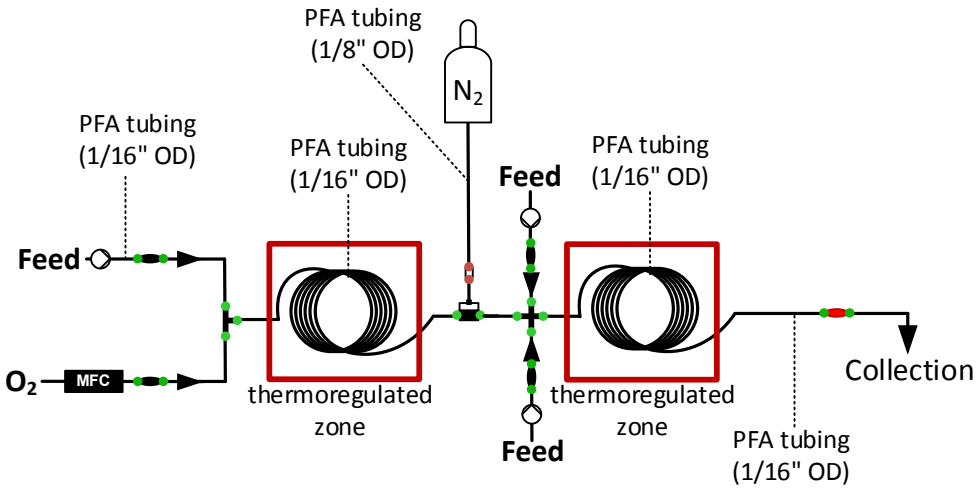


- Super Flangeless Nuts, PEEK 1/4-28 thread for 1/16” OD tubing (+ ferrules)
- Valco SS Nut, standard, for 1/16” OD tubing (+ ferrules)
- HPLC pump
- In-line check valve
- Spring-loaded BPR

Figure S7. Detailed setup for the continuous flow thermolysis of iminol **4a** (heterogeneous conditions)

1.4.8 Concatenated hydroxylation and imination steps (homogeneous conditions)

See manuscript for experimental details (Figure 11).



- Super Flangeless Nuts, PEEK 1/4-28 thread for 1/16” OD tubing (+ ferrules)
- Super Flangeless Nuts, PEEK 1/4-28 thread for 1/8” OD tubing (+ ferrules)
- Pump
- MFC Mass flow controller
- In-line check valve
- T-mixer, natural PEEK 1/4-28 thread for 1/16" OD tubing, 0.02" through hole
- Cross junction natural PEEK 1/4-28 thread for 1/16" OD tubing, 0.02" through hole
- Dome-type back-pressure regulator
- Spring-loaded BPR
- Natural polypropylene standard low pressure union 1/4-28

Figure S8. Detailed setup for concatenated hydroxylation and imination steps (homogeneous conditions)

1.4.9 Concatenated process toward (±)-**1a** and analogs (±)-**1b,c**

See manuscript for experimental details (Figure 11). The last thermoregulated zone includes preheating and cooling loops up- and downstream the packed-bed reactor, respectively (not shown). The surge was flushed with a constant flow of nitrogen gas for venting the excess oxygen.

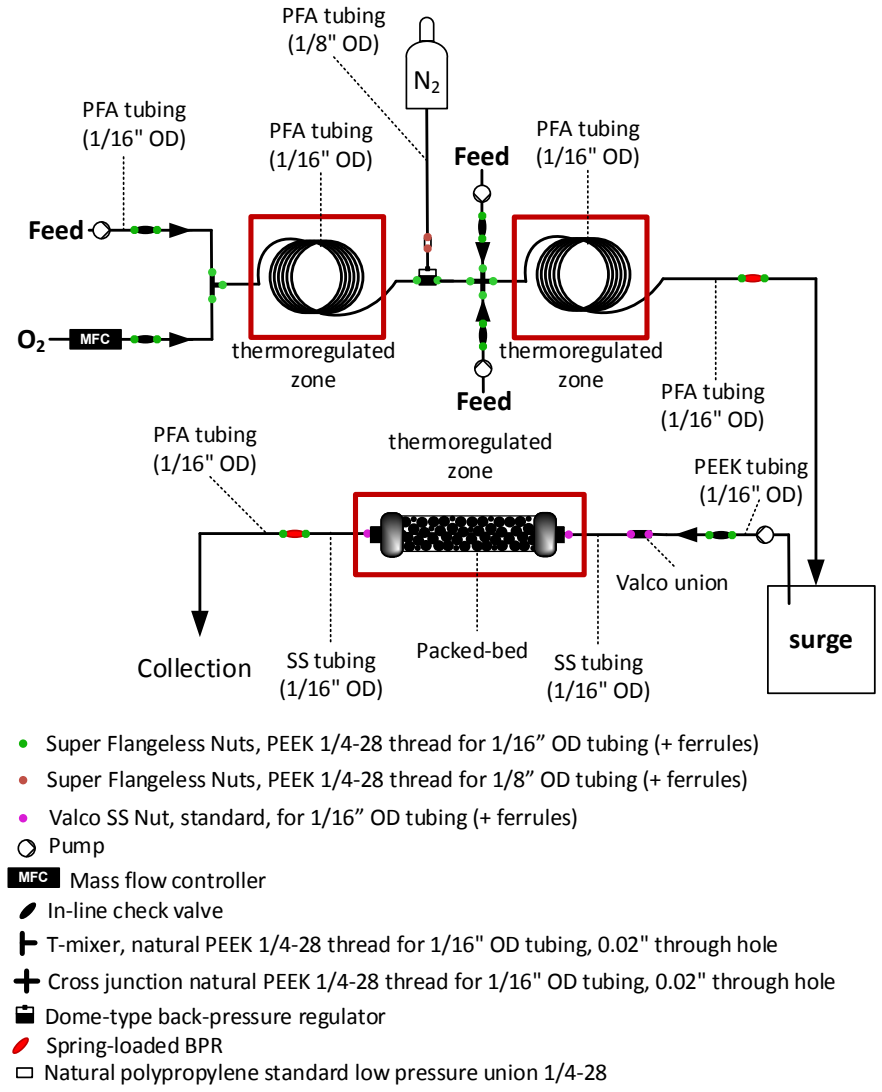


Figure S9. Detailed setup for the concatenated process toward (±)-**1a** and analogs (±)-**1b,c**

2. Additional experimental details

2.1 Chemicals

Chemicals, purity, CAS numbers and suppliers are provided in Table S2.

Table S2. Solvents, chemicals and suppliers

Solvents	Purity (%)	CAS Number	Supplier
Dimethylsulfoxide	>99%	67-68-5	VWR
Ethanol (absolute)	>99%	64-17-5	VWR
Ethyl acetate	≥99.5%	141-78-6	Merck - Sigma Aldrich
1-Ethyl-3-methyl-imidazolium ethyl sulfate [EMIM][ES]	99%	342573-75-5	ALFA AESAR
Methanol	>99%	67-56-1	VWR
2-Methyltetrahydrofuran	≥ 99%	96-47-9	MERCK
Tetrahydrofuran	>99%	203-726-8	VWR
Toluene	99.7%	108-88-3	BIOSOLVE
Chemicals	**Purity (%)**	**CAS number**	**Supplier**
Magnesium (turnings)	>99%	7439-95-4	VWR
Cyclopentylbromide	>98%	137-43-9	TCI
2-Chlorobenzonitrile	>98%	873-32-5	TCI
2-Chlorophenyl cyclopentyl ketone	≥ 98%	6740-85-8	TCI
Tetrakis(acetonitrile) copper (I) hexafluorophosphate	97%	64443-05-6	Merck - Sigma Aldrich
Triethylphosphite	≥ 97%	122-52-1	Merck - Sigma Aldrich
Triethylamine	99%	121-44-8	ACROS ORGANICS
1,8-Diazabicyclo(5.4.0)undec-7-ene (DBU)	>98%	6674-22-2	TCI
tert-Butylimino-tris(pyrrolidino)-phosphorane (BTPP)	≥ 97%	161118-67-8	Merck - Sigma Aldrich
2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP)	≥ 97%	98015-45-3	Merck - Sigma Aldrich
Tetramethyl(tris(dimethylamino)phosphoranylidene)-phosphorictriamid-ethylimine (P2-Et)	>98%	165535-45-5	Merck - Sigma Aldrich
2-*tert*-Butyl-1,1,3,3-tetramethylguanidine (Barton's base)	≥ 97%	29166-72-1	Merck - Sigma Aldrich
2,8,9-Trimethyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane (Verkade's base)	/	120666-13-9	Merck - Sigma Aldrich
tert-Butylimino-tris(dimethylamino)phosphorane (P1-t-Bu)	≥ 97%	81675-81-2	Merck - Sigma Aldrich
tert-Octylimino-tris(dimethylamino)phosphorane (P1-t-Oct)	≥ 97%	16118-69-0	Merck - Sigma Aldrich
Lithium ethoxide 1M in EtOH	/	2388-07-0	Merck - Sigma Aldrich
Sodium ethoxide 21 wt% in EtOH	/	141-52-6	Merck - Sigma Aldrich
Potassium ethoxide 24 wt% in EtOH	/	917-58-8	Merck - Sigma Aldrich
Potassium *tert*butoxide	97%	865-47-4	ALFA AESAR
Tetramethylammonium hydroxide (TMAOH) 25 wt% in MeOH	/	75-59-2	Merck - Sigma Aldrich
Cesium carbonate	99.5%	534-17-8	ACROS ORGANICS
Cesium hydroxide monohydrate	99.95%	35103-79-8	Merck - Sigma Aldrich

Sodium hydroxide	98.5%	1310-73-2	ACROS ORGANICS
Potassium hydroxide	85%	1310-58-3	ACROS ORGANICS
1,4,7,10,13,16-Hexaoxacyclooctadecane (18C6)	99%	17455-13-9	ACROS ORGANICS
1,4,7,10,13-Pentaoxacyclopentadecane (15C5)	98%	33100-27-5	ACROS ORGANICS
1,4,7,10-Tetraoxacyclododecane (12C4)	97%	294-93-9	ACROS ORGANICS
Poly(ethylene glycol) (average Mw 400, PEG-400)	/	25322-68-3	Merck - Sigma Aldrich
Ethanediol (ethylene glycol)	99.8%	107-21-1	ACROS ORGANICS
1,2,3-Propanetriol (glycerol)	99%	56-81-5	ABCR
Phosphazene base P2-t-Bu on polystyrene, (2% cross-linked with DVB)	1.6 mmol g^{-1} loading 100-200 mesh		Merck - Sigma Aldrich
Amberlyst A26 (OH^-)	/	39339-85-0	AlFA AESAR
Dowex Marathon A (OH^-)	/	/	Merck - Sigma Aldrich
Ambersep 900 (OH^-)	/	9017-79-2	AlFA AESAR
Amberlite IRN 78 (OH^-)	/	11128-95-3	AlFA AESAR
Methylamine (33% wt in EtOH)	/	74-89-5	Merck - Sigma Aldrich
Methylamine (40% wt in MeOH)	/	74-89-5	TCI
Methylamine (40% wt in water)	/	74-89-5	Merck - Sigma Aldrich
Ammonia (7 M in MeOH)	/	7664-41-7	Merck - Sigma Aldrich
Benzylamine	99%	100-46-9	Janssen Chimica
Trimethyl borate	99%	121-43-7	ACROS ORGANICS
Triethyl borate	>97%	150-46-9	TCI
Triisopropyl borate	>98%	5419-55-6	TCI
Boron trifluoride diethyl ether complex	>98%	109-63-7	TCI
Titanium (IV) isopropoxide	>98%	546-68-9	ACROS ORGANICS
Montmorillonite K10	/	1318-93-0	ACROS ORGANICS
Hydrochloric acid (5-6N in isopropanol)	/	7647-01-0	ACROS ORGANICS
Hydrochloric acid (3 M in *n*-BuOH)	/	7647-01-0	Merck - Sigma Aldrich
Hydrochloric acid (2 M in Et_2O)	/	7647-01-0	Merck - Sigma Aldrich
Oxygen	alpha 1		Air Liquide
Air	alpha 1		Air Liquide

2.2 Additional experimental data

2.2.1 Batch procedure for the synthesis of (2-chlorophenyl)cyclopentyl ketone (**2**)

A magnetic stir bar, a small crystal of iodine, magnesium turnings (9.90 g, 0.407 mol, 1 equiv.) and dry THF (150 mL) were added in a flame-dried three-neck round-bottom flask equipped with a reflux condenser and a dropping funnel under a nitrogen atmosphere. A solution of bromocyclopentane (43.4 mL, 0.405 mol, 1 equiv.) in dry THF (100 mL) was added dropwise to the stirred suspension of Mg over 3 h at room temperature. Meanwhile, *o*-chlorobenzonitrile (55.7 g, 0.405 mol, 1 equiv.), $[(CH_3CN)_4Cu]PF_6$ (1.51 g, 0.004 mol, 0.01 equiv.) and dry THF (200 mL) were added in a flame-dried two-neck round-bottom flask under a nitrogen atmosphere. The stirred solution of the Grignard reagent was cooled down to 0 °C, and to it was transferred the solution of *o*-chlorobenzonitrile through a cannula. The resulting mixture was refluxed for 12 h under nitrogen. Then, the reaction medium was cooled down to 0 °C and diluted by (careful) addition of water (100 mL) and aqueous H_2SO_4 (15%, 400 mL). The mixture was allowed to evolve to room temperature, and stirred for 6 h. The reaction mixture was extracted with 5 x 200 mL of *n*-pentane. The organic phases were combined, dried over $MgSO_4$, filtered over silica gel, and the solvent was removed under reduced pressure. The resulting crude material was purified by vacuum distillation, affording (2-chlorophenyl)(cyclopentyl)methanone as a transparent oil (21.7 g, 26%).

2.2.2 Optimization of the hydroxylation of ketone **2** under homogeneous conditions

2.2.2.1 Screening of bases

Table S3. Process optimization for the continuous flow hydroxylation of **2** in EtOH with various bases.

Entry[a]	Base	[Base] (mol-%)	T (°C)	P (bar)	Conv. (%)[b]	Selec. for **7** (%)[b]
1	DBU	100	40	5	0	0
2	DBU	100	60	5	0	0
3	DBU	100	80	5	0	0
4	DBU	100	100	5	0	0
5	DBU	100	120	5	0	0
6	Et_3N	100	60	5	0	0
7	Et_3N	100	80	5	0	0
8	Et_3N	100	100	5	0	0
9	Cs_2CO_3	20	25	5	12	95
10	Cs_2CO_3	20	60	5	34	37
11	Cs_2CO_3	20	60	10	50	34
12	Barton	20	60	10	6	74

13	Barton	20	80	10	6	74
14	Barton	20	100	10	6	74
15	Verkade	20	40	10	20	96
16	Verkade	20	60	10	41	90
17	BEMP	20	60	10	8	99
18	P_1-*t*Bu	20	40	10	9	99
19	P_1-*t*Bu	20	60	10	13	99
20	P_1-*t*-Oct	20	40	10	7	99
21	P_1-*t*-Oct	20	60	10	10	99
22	P_2-Et	20	60	10	50	87
23	P_2-Et	20	80	10	54	60
24	P_2-Et	20	100	10	60	60
25	P_2-Et	20	120	10	52	62
26[c]	P_2-Et	20	120	10	41	55
27	*t*BuOK	20	60	10	46	17
28[c]	*t*BuOK	20	60	10	71	42
29	*t*BuOK	100	60	10	99	5
30[d]	*t*BuOK	20	60	10	48	71

[a] Typical conditions: residence time = 5 min; concentration of **2** in the feed solution = 0.5 M; 1.1 equiv. of $P(OEt)_3$; liquid flow rate = 0.2 mL min^{-1}, O_2 flow rate = 3 mL_n min^{-1}. [b] Conversion and yield were determined by HPLC/DAD processed at 220 nm. [c] O_2 flow rate = 5 mL_n min^{-1}. [d] addition of 18-C-6 (20 mol%).

2.2.2.2 Optimization of the hydroxylation with *t*BuOK as a base

Table S4. Process optimization for the continuous flow hydroxylation of **2** (0.5 M) in EtOH with *t*-BuOK.

Entry[a]	[Base] & [Additive] (mol%)	Liquid flow rate (mL min^{-1})	O_2 flow rate (mL_n min^{-1})	T (°C)	P (bar)	Conv. (%)[b]	Selec. for **7** (%)[b]
1[c]	50	0.2	3	60	10	95	7
2	50	0.1	3	25	10	48	94
3	50	0.1	3	60	10	99	44
4	50	0.2	3	60	10	99	48
5	50	0.2	3	25	17	65	95
6	50	0.2	3	40	17	92	83
7	20	0.2	10	25	10	11	99
8	20	0.2	10	40	10	11	92
9	50	0.2	10	25	11	25	98
10	50	0.2	10	40	11	55	92
11	50	0.2	10	50	11	75	84

[a] Typical conditions: residence time = 5 min; concentration of **2** in the feed solution = 0.5 M; 1.1 equiv. of $P(OEt)_3$; base = *t*BuOK; additive = 18-C-6. [b] Conversion and yield were determined by HPLC/DAD processed at 220 nm. [c] No additive.

2.2.2.3 Impact of the amount of *t*BuOK as a base

Table S5. Process optimization for the continuous flow hydroxylation of **2** (1 M) in EtOH with *t*-BuOK.

Entry[a]	[Base] & [Additive] (mol%)	T (°C)	Conv. (%)[b]	Selec. for **7** (%)[b]
1	50	20	97	98
2	50	30	99	96
3	50	40	99	82
4	50	50	99	68
5	50	60	99	60
6[c]	50	20	93	98
7[c]	50	30	95	98
8[d]	50	25	77	70
9[d]	50	30	83	60
10[d]	50	35	95	50
11	100	25	99	25
12	10	25	14	94
13	10	30	20	96
14	10	35	21	97
15	5	25	5	99
16	5	30	6	99
17	5	35	7	99
18	5	40	8	99
19	1	25	<1	99
20	1	30	<1	99
21	1	35	<1	99
22	1	40	<1	99

[a] Typical conditions: residence time = 5 min; concentration of **2** in the feed solution = 1 M; 1.1 equiv. of $P(OEt)_3$; P = 11 bar; liquid flow rate = 0.2 mL.min^{-1}; O_2 flow rate = 10 mL min^{-1}, [b] Conversion and yield were determined by HPLC/DAD processed at 220 nm. [c] No additive. [d] O_2 flow rate = 20 mL min^{-1}.

2.2.2.4 Influence of the countercation

Table S6. Process optimization for the continuous flow hydroxylation of **2** (1 M) in EtOH - Influence of the counter-cation.

Entry[a]	Base	T (°C)	Conv. (%)[b]	Selec. for **7** (%)[b]
1	EtOLi	25	32	10
2	EtOLi	30	33	8
3	EtOLi	35	36	6
4	EtOLi	40	40	5
5	EtOLi	45	43	3
6	EtONa	20	96	74
7	EtONa	25	99	72
8	EtONa	30	99	68
9	EtONa	35	99	61
10	EtONa	40	99	54
11	EtOK	20	98	96
12	EtOK	25	99	95
13	EtOK	30	99	90
14	EtOK	35	99	87
15	EtOK	40	99	82

[a] Typical conditions: residence time = 5 min; concentration of **2** in the feed solution = 1 M; 1.1 equiv. of $P(OEt)_3$; P = 11 bar; liquid flow rate = 0.2 mL min^{-1}, O_2 flow rate = 10 mL_n min^{-1}. The additives for EtOLi, EtONa and EtOK are 12-C-4, 15-C-5 and 18-C-6, respectively. The concentration of base and additive was set to 50 mol%. [b] Conversion and yield were determined by HPLC/DAD processed at 220 nm.

2.2.2.5 Continuous flow hydroxylation of **2** with phosphazene bases

Table S7. Process optimization for the continuous flow hydroxylation of **2** (1 M) in EtOH with phosphazenes

Entry[a]	Base	T (°C)	Conv. (%)[b]	Selec. for **7** (%)[b]
1	BTPP	25	40	99
2	BTPP	30	46	99
3	BTPP	35	50	99
4	BTPP	40	58	99
5	P_2Et	25	95	98
6	P_2Et	30	98	98
7	P_2Et	35	99	96
8	P_2Et	40	99	94

[a] Typical conditions: residence time = 5 min; concentration of **2** in the feed solution = 1 M; 1.1 equiv. of $P(OEt)_3$; P = 11 bar; liquid flow rate = 0.2 mL min^{-1}, O_2 flow rate = 10 mL_n min^{-1}. The concentration of base was set to 50 mol%. [b] Conversion and yield were determined by HPLC/DAD processed at 220 nm.

2.2.2.6 Continuous flow hydroxylation of **2** with alkaline hydroxides

Table S8. Process optimization for the continuous flow hydroxylation of **2** (1 M) in EtOH with various alkaline hydroxides

Entry[a]	Base	T (°C)	Conv. (%)[b]	Selec. for **7** (%)[b]
1	NaOH	25	88	69
2	NaOH	30	91	63
3	NaOH	35	93	55
4	NaOH	40	94	49
5	KOH	25	96	97
6	KOH	30	97	96
7	KOH	35	99	94
8	KOH	40	99	92
9[c]	KOH	25	85	71
10[c]	KOH	30	88	64
11[c]	KOH	35	90	60

12[c]	KOH	40	91	57
13[c]	TMAOH	25	55	97
14[c]	TMAOH	30	63	97
15[c]	TMAOH	35	76	95
16[c]	TMAOH	40	85	92
17[c,d]	TMAOH	20	93	95
18[c,d]	TMAOH	25	95	95
19[c,d]	TMAOH	30	99	91
20[c,d]	TMAOH	35	99	89
21	CsOH	20	99	92
22	CsOH	25	99	89
23[e]	CsOH	20	99	96
24[e]	CsOH	25	99	96
25[e]	CsOH	30	99	94
26[e]	CsOH	35	99	93

[a] Typical conditions: residence time = 5 min; concentration of **2** in the feed solution = 1 M; 1.1 equiv. of $P(OEt)_3$; P = 11 bar; liquid flow rate = 0.2 mL min^{-1}, O_2 flow rate = 10 mL_n min^{-1}. The concentration of base and additive was set to 50 mol%. The additive for NaOH is 15-C-5; the additive for KOH and CsOH is 18-C-6. [b] Conversion and yield were determined by HPLC/DAD processed at 220 nm. [c] No additive. [d] The concentration of base was set to 100 mol%.[e] The concentration of the additive was set to 100 mol%.

2.2.2.7 Impact of the cation-chelating additives on the hydroxylation reaction

Table S9. Process optimization for the continuous flow hydroxylation of **2** (1 M) in EtOH with various cation-chelating additives

Entry[a]	Additives	T (°C)	Conv. (%)[b]	Selec. for **7** (%)[b]
1	PEG-400	20	94	99
2	PEG-400	25	94	99
3	PEG-400	30	99	95
4	PEG-400	35	99	90
5	PEG-400	40	99	86
6[c]	PEG-400	25	99	99
7[c]	PEG-400	30	99	92
8	PEG(-OMe)-550	25	99	94
9	PEG(-OMe)-550	30	99	93
10	PEG(-OMe)-550	35	99	89
11	PEG(-OMe)-550	40	99	84
12	Ethylene glycol	25	45	89
13	Ethylene glycol	30	46	86
14	Ethylene glycol	35	47	88
15	Ethylene glycol	40	50	80
16	Glycerol	25	37	88
17	Glycerol	30	46	83
18	Glycerol	35	49	81

[a] Typical conditions: residence time = 5 min; concentration of **2** in the feed solution = 1 M; 1.1 equiv. of $P(OEt)_3$; P = 11 bar, liquid flow rate = 0.2 mL min^{-1}, O_2 flow rate = 10 mL_n min^{-1}. The concentration of KOH and additive was set to 50 mol%. [b] Conversion and yield were determined by HPLC/DAD processed at 220 nm. [c] The concentration of additive was set to 100 mol%.

2.2.2.8 Continuous flow hydroxylation of **2** with air.

Table S10. Continuous flow hydroxylation of **2** (1 M) in EtOH with air

Entry[a]	T (°C)	Conv. (%)[b]	Selec. for **7** (%)[b]
1	25	13	98
2	30	14	97
3	35	14	95
4	40	17	85

[a] Typical conditions: residence time = 5 min; concentration of **2** in the feed solution = 1 M; 1.1 equiv. of $P(OEt)_3$; P = 11 bar; liquid flow rate = 0.2 mL min^{-1}, air flow rate = 10 mL_n min^{-1}. The concentration of KOH and PEG-400 was set to 50 mol%. [b] Conversion and yield were determined by HPLC/DAD processed at 220 nm.

2.2.2.9 Batch hydroxylation of **2** using Jiao's procedure

(2-Chlorophenyl)(cyclopentyl)methanone (**2,** 40 g, 0.192 mol, 1 equiv.), triethylphosphite (35 g, 0.211 mol, 1.1 equiv.), cesium carbonate (12.5 g, 0.038 mol, 0.2 equiv.), DMSO (200 mL) and a magnetic stir bar were charged in a round-bottom flask. The reaction mixture was stirred for 12 h at room temperature under an oxygen atmosphere. The medium was diluted with 500 mL of brine, filtered and extracted with 4 x 200 mL of diethyl ether. The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography on silica gel (ethyl acetate/petroleum spirit 1:1), affording (2-chlorophenyl)(1-hydroxycyclopentyl)methanone (**7**) as a yellow oil (34.3 g, 80%).[S1]

2.2.2.10 Batch hydroxylation of **2** and **mod-2** using Jiao's procedure

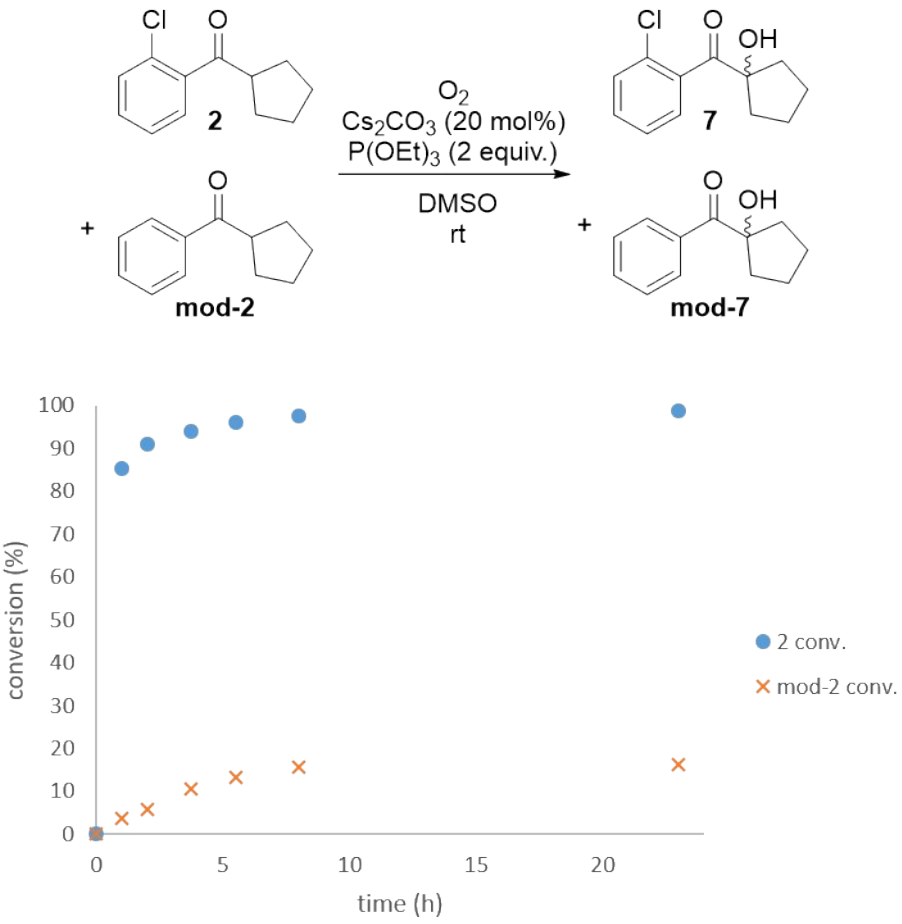
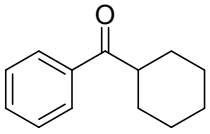


Figure S10. Evolution of **2** and **mod-2** conversion as a function of time using Jiao's batch procedure.[S1] Conditions: 9.37 mmol of **2**, 3.12 mmol of **mod-2**, 25 mmol of $P(OEt)_3$, 2.5 mmol of Cs_2CO_3, 50 mL of DMSO, O_2 atmosphere, room temperature. Conversion was determined by HPLC/DAD processed at 220 nm.

2.2.2.11 Continuous flow hydroxylation on other substrates

The continuous flow setup utilized for the hydroxylation of other substrates is depicted on Figure 3a in the manuscript.

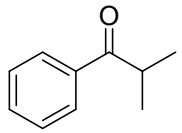


cyclohexyl(phenyl)methanone

Table S11. Continuous flow hydroxylation of cyclohexyl(phenyl)methanone (1 M) in EtOH

Entry[a]	Bases	T (°C)	Conv. (%)[b]	Selec. (%)[b]
1	KOH	25	0	0
2	KOH	30	0	0
3	KOH	35	0	0
4	KOH	40	0	0
5	*t*-BuOK	25	<1	99
6	*t*-BuOK	30	<1	99
7	*t*-BuOK	35	<1	99
8	*t*-BuOK	100	36	99
9	*t*-BuOK	110	36	99
10	*t*-BuOK	120	33	99
11	*t*-BuOK	130	31	99

[a] Typical conditions: residence time = 5 min; concentration of substrate in the feed solution = 1 M; 1.1 equiv. of $P(OEt)_3$; P = 11 bar; liquid flow rate = 0.2 mL min^{-1}, O_2 flow rate = 10 mL_n min^{-1}. The concentration of the base and PEG-400 was set to 50 mol%. [b] Conversion and yield were determined by HPLC/DAD processed at 220 nm.



2-methyl-1-phenylpropan-1-one

Table S12. Continuous flow hydroxylation of 2-methyl-1-phenylpropan-1-one (1 M) in EtOH

Entry[a]	Bases	T (°C)	Conv. (%)[b]	Selec. (%)[b]
1	KOH	25	3	99
2	KOH	30	5	99
3	KOH	35	7	99
4	KOH	40	9	99
5	*t*-BuOK	25	18	99
6	*t*-BuOK	40	40	99
7	*t*-BuOK	60	53	99
8[c]	*t*-BuOK	80	55	99
9[c,d]	*t*-BuOK	25	n.a.	n.a.

[a] Typical conditions: residence time = 5 min; concentration of substrate in the feed solution = 1 M; 1.1 equiv. of $P(OEt)_3$; P = 11 bar; liquid flow rate = 0.2 mL min^{-1}, O_2 flow rate = 10 mL_n min^{-1}. The concentration of the base and PEG-400 was set to 50 mol%. [b] Conversion and yield were determined by HPLC/DAD processed at 220 nm. [c] Reactor clogging was observed. [d] The amount of the base and PEG-400 was set to 1 equiv.

2.2.3 Optimization of the hydroxylation of ketone **2** under heterogeneous conditions

Table S13. Process optimization for the heterogeneous hydroxylation of ketone **2** with polystyrene-supported phosphazene P2-t-Bu.

Entry[a]	[**2**] (M)	Liquid flow rate (mL min^{-1})	T (°C)	Conv. (%)[b]	Selec. (%)[b]
1	0.5	0.2	40	0	/
2	0.5	0.2	60	1	>99
3	neat	0.05	60	7	>99

[a] Typical conditions: 2 equiv. of $P(OEt)_3$; P = 8.5 bar; O_2 flow rate = 3 mL_n min^{-1}, volume of the bed = 1.6 cm^3 (200 mg of PS-P_2-*t*-Bu diluted with 1 g of glass bead). [b] Conversion and selectivity were determined after 60 min of equilibration, by HPLC/DAD processed at 220 nm.

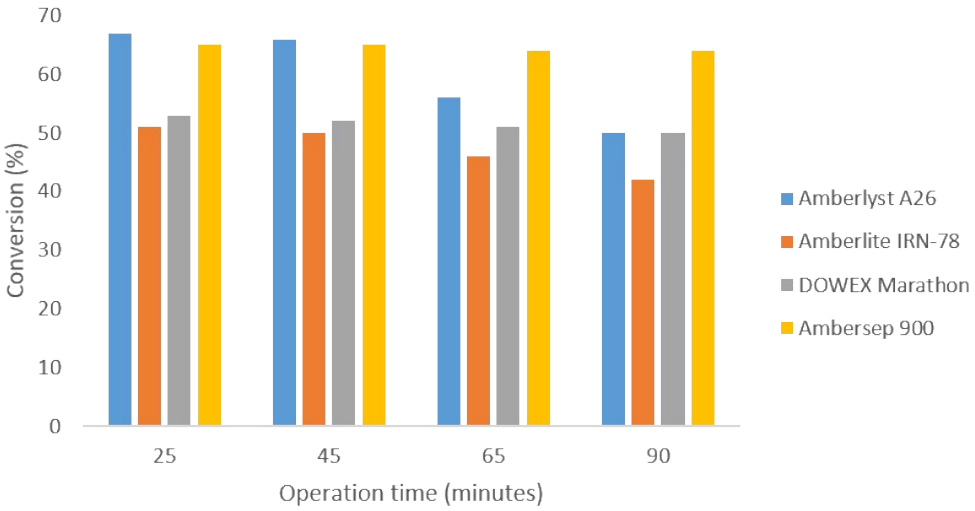


Figure S11. Evolution of the conversion over time for the heterogeneous hydroxylation of ketone **2** as a function of the heterogeneous catalyst nature. Conditions: concentration of **2** in the feed solution = 0.5 M; 2 equiv. of $P(OEt)_3$; T = 25 °C; P = 8.5 bar; liquid flow rate = 0.2 mL min^{-1}; O_2 flow rate = 3 mL_n min^{-1}; volume of the catalyst bed = 1.6 cm^3. Conversion and yield were determined by HPLC/DAD processed at 220 nm. Selectivity for **7** is > 92% for each data point (not plotted).

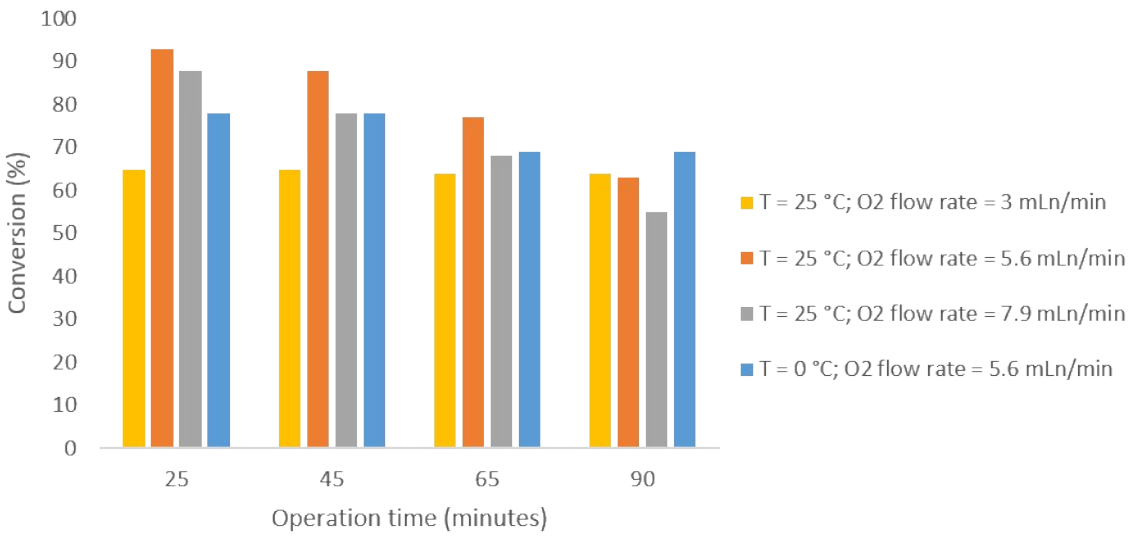


Figure S12. Evolution of the conversion over time for the Ambersep 900-catalyzed hydroxylation of ketone **2** as a function of the reaction conditions. Conditions: concentration of **2** in the feed solution = 0.5 M; 2 equiv. of $P(OEt)_3$; P = 8.5 bar; liquid flow rate = 0.2 mL min^{-1}; volume of the Ambersep 900 catalytic bed = 1.6 cm^3. Conversion and yield were determined by HPLC/DAD processed at 220 nm. Selectivity for **7** is > 92% for each data point at 25 °C, and > 98% for each data point at 0 °C (not plotted).

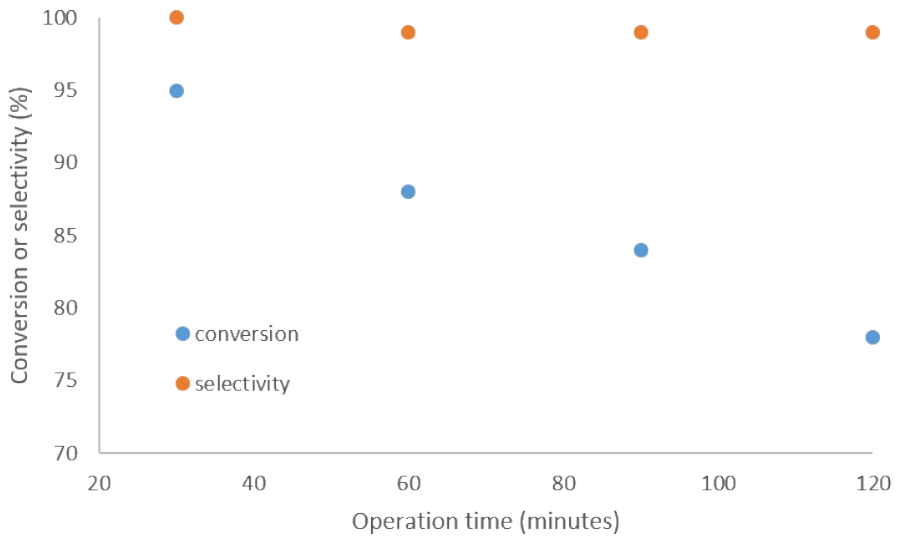
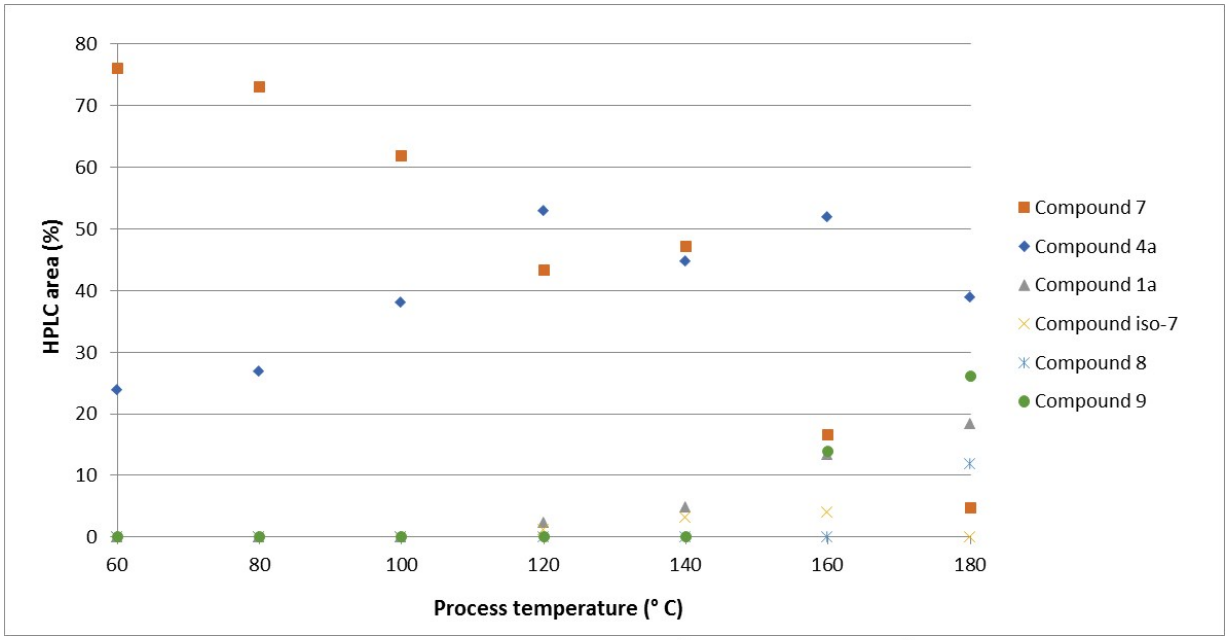


Figure S13. Evolution of the conversion and selectivity for **7** over time for the Ambersep 900-catalyzed hydroxylation of ketone **2** under optimized conditions. Conditions: concentration of **2** in the feed solution = 0.5 M; 2 equiv. of $P(OEt)_3$; T = 0 °C; P = 8.5 bar; liquid flow rate = 0.15 mL min^{-1}; O_2 flow rate = 4.2 mL_n min^{-1}; volume of the Ambersep 900 catalytic bed = 1.6 cm^3. Conversion and yield were determined by HPLC/DAD processed at 220 nm.

2.2.4 Imination of (±)-(2-chlorophenyl)(1-hydroxycyclopentyl)methanone (**7**) under continuous flow conditions without additive



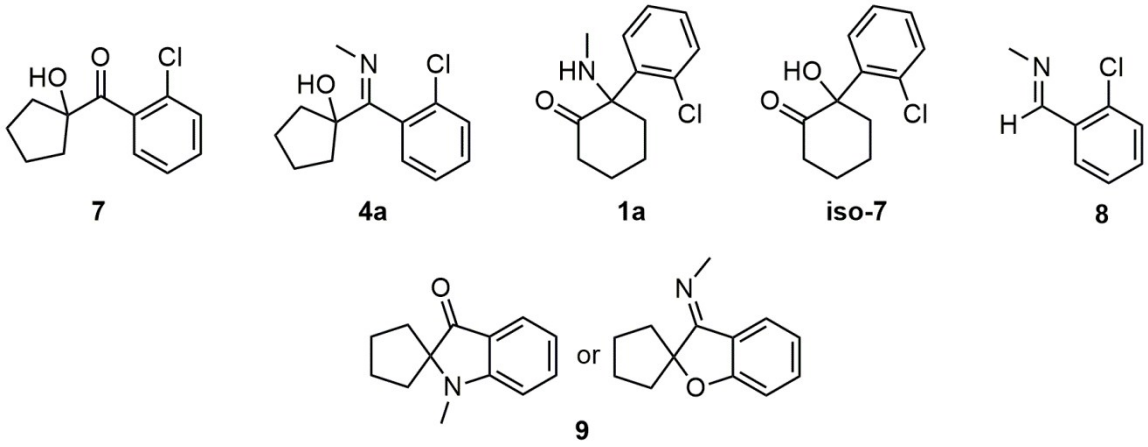


Figure S14. Reaction profile for the imination of **7** (HPLC/DAD processed at 216 nm). The preliminary optimization for the imination of **7** (0.5 M in EtOH) with $MeNH_2$ (5 equiv.) toward the formation of hydroxyimine **4a** was studied in a SS coil (60-180 °C, 17 bar, 10 min of residence time). The structure of compound **9** is based on HRMS analysis (Figure S15) and its UV absorption profile.[S2]

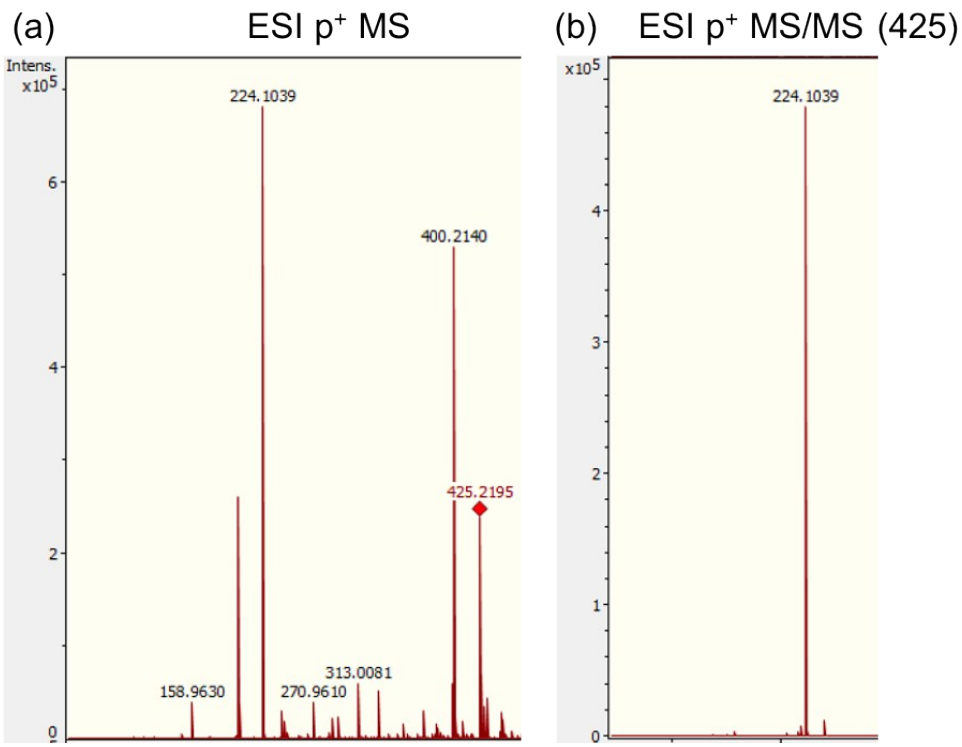


Figure S15. MS analysis of compound **9**. The material was isolated from a crude effluent from the imination reaction at 180 °C by micropreparative HPLC/DAD. ESI HRMS/MS (425) *m/z* $C_{13}H_{15}NO^+$ $[M+Na]^+$: calcd 224.1045; found 224.1039.

2.2.5 Batch procedure for the synthesis of α-iminol **4a**

To a mixture of (2-chlorophenyl)(1-hydroxycyclopentyl)methanone (**7**, 8.78 g, 0.039 mol, 1 equiv.) and triisopropyl borate (18 mL, 0.078 mol, 2 equiv.) was added dropwise a solution of methylamine 33 wt % in EtOH (10 mL, 0.080 mol, 2.05 equiv.) under stirring at room temperature. After 1 h, the reaction medium was diluted with 250 mL of saturated aqueous Na_2CO_3, and extracted with 3 x 250 mL of ethyl acetate. The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. 1-((2-Chlorophenyl)(methylimino)methyl)cyclopentan-1-ol (**4a**) was obtained as a white-brownish solid (8.35 g, 90%).

2.2.6 Concatenated two-step continuous flow process toward α-iminol **4a** (microfluidic setup)

The syringe pump used to deliver the solution of 2-chlorophenyl cyclopentyl ketone (**2**, 1 M), KOH (0.5 M), PEG-400 (1 M) and $P(OEt)_3$ (1.1 M) in EtOH) was set to 0.25 mL min^{-1}. Oxygen was delivered using a mass flow controller set to 10 mL min^{-1} and both streams were mixed through a PEEK T-mixer. The reaction mixture entered a first PFA capillary coil (5 min of residence time) operated at 25°C under 12 bar. The outlet of the back-pressure regulator was connected to a PEEK cross junction with Super Flangeless nuts and ferrules. A neat solution of triisopropyl borate was delivered by a second syringe pump, set to 0.13 mL min^{-1} (2 equiv.) while a solution of methylamine (33 wt. % in EtOH) was delivered by a third syringe pump, set to 0.05 mL min^{-1} (1.5 equiv.). The second and third syringe pumps were connected to the PEEK cross junction, and the resulting mixture was then redirected to a second PFA capillary coil (2 min of residence time) operated at 25 °C under 7 bar. The reactor effluent was collected at steady state, diluted in EtOH, and analyzed by HPLC/DAD (99% conversion, 97% selectivity for **4a**). Alternatively, the feed solution of methylamine was changed to ammonia in MeOH (7 M, 0.29 mL min^{-1}) or benzylamine (neat, 0.04 mL min^{-1}) to afford compounds **4b** (conv. = 55%, selec. = 98%) or **4c** (conv. = 99%, selec. = 99%), respectively.

2.2.7 Preliminary optimization for the thermal rearrangement of α-iminol **4a** under microwave conditions

The preliminary optimization under microwave conditions was realized with a CEM microwave reactor. The reactor vessel was loaded with 0.1 g of **4a** (0.42 mmol), 0.1 g (100 wt.-%) of additive (K10) in 1 mL of absolute EtOH.

Table S14. Process optimization for the thermal rearrangement of α-iminol **4a** in ethanol (homogenous conditions) in a microwave reactor.

Entry[a]	T (°C)	P (bar)	Power (W)	t (min)	Yield (%)[b]
1	150	8.5	150	5	10
2	160	10	150	5	18
3	170	16	150	5	33
4	180	20	150	5	56

[a] Typical conditions: [**4a**] = 0.42 M. [b] Conversion and yield were determined by HPLC/DAD processed at 216 nm.

Table S15. Process optimization for the thermal rearrangement of α-iminol **4a** in ethanol (heterogeneous conditions with additive or HCl) in a microwave reactor.

Entry[a]	T (°C)	P (bar)	Power (W)	t (min)	Conv. (%)[b]
1	140	8	300	15	23
2	160	10	300	15	56
3	180	20	300	15	70
4	180	20	300	20	75
5	180	20	300	30	80
6[c]	180	20	300	15	60
7[d]	180	20	300	15	<1
8	180	20	150	15	81
9[e]	170	20	150	15	99[f]
10	180	20	150	10	79
11	180	20	150	5	77
12	180	20	150	2.5	67
13	160	20	150	2.5	37
14[g]	180	20	150	5	40
15[h]	200	10	300	5	75

16[h]	220	15	300	5	73
17[h]	240	20	300	5	60
18[i]	180	20	300	15	57

[a] Typical conditions: [**4a**] = 0.42 M; 100 wt% K10. [b] Conversion and yield were determined by HPLC/DAD processed at 216 nm. Unless specified, selectivity towards **1a**: >99%. [c] Addition of 1 equiv. of B(O*i*Pr)$_3$. [d] Reaction performed in neat B(O*i*Pr)$_3$. [e] addition of HCl (1 M in EtOH, 1.1 equiv.). [f] selectivity towards **1a**: 55%. [g] Addition of 100 mol-% of KOH. [h] Reaction performed in 1-butanol. [i] [**4a**] = 1 M.

2.2.8 Preliminary optimization for the thermal rearrangement of α-iminol **4a** under continuous flow homogeneous conditions

Table S16. Process optimization for the thermal rearrangement of α-iminol **4a** in ethanol under homogeneous conditions without HCl or additives.

Entry[a]	[**4a**] (M)	T (°C)	P (bar)	Conv. (%)[b]	Selec. for **1a** (%)[b]	Selec. for **8** (%)[b]
1	0.42	150	22	3	91	traces
2	0.42	160	22	8	85	traces
3	0.42	170	22	18	87	4
4	0.1	180	22	31	87	7
5	0.42	180	22	33	89	6
6	0.1	200	35	66	80	12
7	0.42	200	35	63	84	10
8	0.1	220	35	62	75	18
9	0.42	220	35	71	78	15
10	0.1	240	35	71	81	15
11	0.42	240	35	75	77	12
12	0.1	240	50	79	63	25

[a] Typical conditions: residence time = 5 min. [b] Conversion and yield were determined by HPLC/DAD processed at 216 nm.

2.2.9 Preliminary optimization for the thermal rearrangement of α-iminol **4a** under continuous flow heterogeneous conditions

Table S17. Process optimization for the thermal rearrangement of α-iminol **4a** under heterogeneous conditions, in different solvents, and in the presence or absence of additives.

Entry[a]	Solvent	Additive	Flow rate (mL min^{-1})	T (°C)	Conv. (%)[b]	Selec. for **1a** (%)[b]	Selec. for **8** (%)[b]
1	EtOH	none	0.8	180	76	96	traces
2	EtOH	none	1.6	180	75	95	traces
3[c]	EtOH	none	1.6	180	75	96	traces
4[d]	EtOH	none	0.8	180	69	89	traces
5[d]	EtOH	none	1.6	180	57	91	traces
6	EtOH	$B(OiPr)_3$	1.6	180	73	96	traces
7	[EMIM][ES]	none	1.6	180	26	94	traces
8	DMSO	none	1.6	180	16	69	9
9	MeTHF	none	1.6	180	73	89	traces
10	toluene	none	1.6	180	75	92	traces
11	EtOH	none	0.8	200	75	85	traces
12	EtOH	none	1.6	200	75	91	traces
13	EtOH	$B(OiPr)_3$	1.6	200	73	92	traces
14	[EMIM][ES]	none	1.6	200	40	85	traces
15	DMSO	none	1.6	200	30	69	12
16	MeTHF	none	1.6	200	73	81	traces
17	toluene	none	1.6	200	78	68	5
18	EtOH	none	0.8	220	78	67	4
19	EtOH	none	1.6	220	75	83	4
20	EtOH	$B(OiPr_3)$	1.6	220	73	84	3
21	DMSO	none	1.6	220	58	50	16
22	MeTHF	none	1.6	220	77	58	4
23	toluene	none	1.6	220	85	44	6

[a] Typical conditions: [**4**] = 0.1 M; [additive] = 0.2 M; P = 35 bar; 3.7 g of montmorillonite K10 in the packed-bed. [b] Conversion and yield were determined after injection of 50 mL of feedstock solution through the packed-bed, by HPLC/DAD processed at 216 nm. [c] P = 55 bar. [d] [**4**] = 0.42 M.

2.2.10 Concatenated three-step continuous flow process toward (±)-ketamine (**1a**) (microfluidic setup)

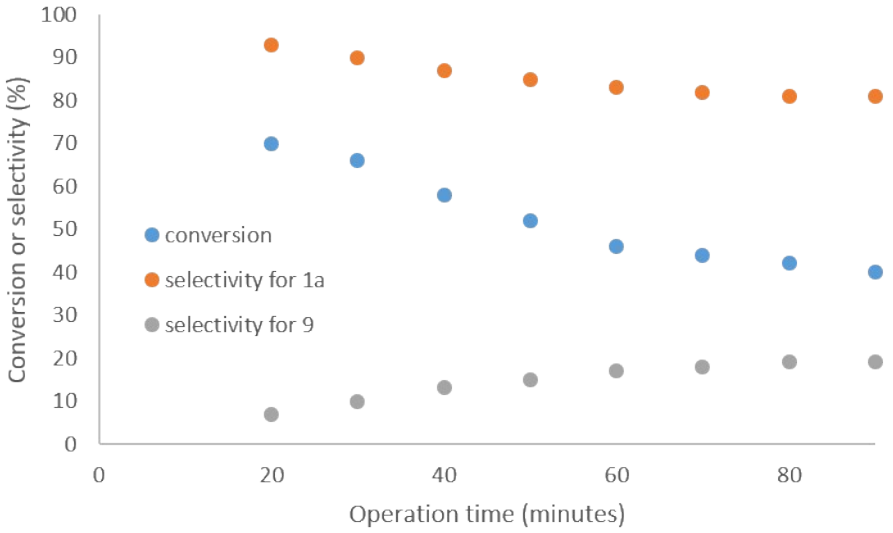
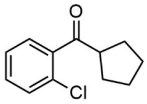


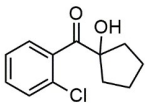
Figure S16. Evolution of **4a** conversion and of the selectivities for (±)-ketamine (**1a**) and compound **9** over time for the concatenated three-step continuous flow process toward **1a**. Conditions (flow rates, concentrations, temperatures, pressures and design of the reactors) are described in the experimental section of the manuscript. Conversion and yields were determined by HPLC/DAD processed at 216 nm.

2.3 Characterization of compounds



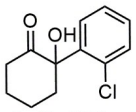
$C_{12}H_{13}ClO$
MW 208.69

(2-chlorophenyl)(cyclopentyl)methanone (2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.43-7.26 (m, 4H), 3.58 (p, J = 7.9 Hz, 1H), 1.94-1.82 (m, 4H), 1.78-1.56 (m, 4H) ppm. **^{13}C NMR ($CDCl_3$, 100.6 MHz):** δ = 206.9, 140.4, 131.2, 130.8, 130.4, 128.6, 126.9, 51.1, 29.6, 26.1 ppm. **IR (neat)**: ν_{max} = 2953, 2868, 1693, 1589 cm^{-1}. **ESI HRMS** *m/z* $C_{12}H_{14}ClO^+$ $[M+H]^+$: calcd 209.0728; found 209.0729.



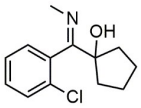
$C_{12}H_{13}ClO_2$
MW 224.68

(±)-(2-chlorophenyl)(1-hydroxycyclopentyl)methanone (7). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.45-7.23 (m, 4H), 3.26 (s, 1H), 2.21-2.08 (m, 2H), 1.99-1.84 (m, 4H), 1.82-1.68 (m, 2H) ppm. **^{13}C NMR ($CDCl_3$, 100.6 MHz):** δ = 209.5, 138.4, 130.8, 130.4, 130.1, 127.3, 126.5, 88.6, 39.4, 24.5 ppm. **ESI HRMS** *m/z* $C_{12}H_{13}ClO_2Na^+$ $[M+Na]^+$: calcd 247.0496; found 247.0495.



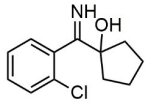
$C_{12}H_{13}ClO_2$
MW 224.68

(±)-2-(2-chlorophenyl)-2-hydroxycyclohexan-1-one (iso-7). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.69 (dd, J = 7.8, 1.6 Hz, 1H), 7.44-7.23 (m, 3H), 4.51 (s, 1H), 3.08-2.91 (m, 1H), 2.72-2.55 (m, 1H), 2.54-2.40 (m, 1H), 2.15-2.04 (m, 1H), 1.90-1.69 (m, 4H) ppm. **^{13}C NMR ($CDCl_3$, 100.6 MHz):** δ = 212.6, 137.5, 134.0, 131.3, 129.7, 128.6, 127.1, 80.6, 41.9, 38.8, 29.5, 22.8 ppm. The ^{13}C NMR data matched those reported in the literature.[S3] **IR (neat)**: ν_{max} = 3384, 1700 cm^{-1}. **ESI HRMS** *m/z* $C_{12}H_{13}ClO_2Na^+$ $[M+Na]^+$: calcd 247.0496; found 247.0494. The NMR spectra were recorded on the crystals used for X-ray structure determination.



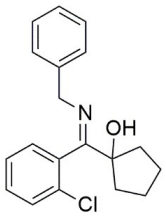
$C_{13}H_{16}ClNO$
MW 237.73

(±)-1-((2-chlorophenyl)(methylimino)methyl)cyclopentan-1-ol (4a). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.47-7.42 (m, 1H), 7.37-7.27 (m, 2H), 7.10-7.04 (m, 1H), 5.53 (s, 1H), 3.01 (s, 3H), 2.00-1.52 (m, 8H) ppm. **^{13}C NMR ($CDCl_3$, 100.6 MHz):** δ = 173.1, 134.2, 132.2, 130.0, 129.1, 126.7, 84.4, 39.5, 38.4, 38.1, 23.7, 23.6 ppm. **IR (neat)**: ν_{max} = 3307, 2967, 2869, 1648, 1389 cm^{-1}. **ESI HRMS** *m/z* $C_{13}H_{17}ClNO^+$ $[M+H]^+$: calcd 238.0993; found 238.0994.



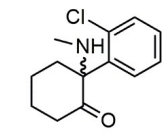
$C_{12}H_{14}ClNO$
MW 223.70

(±)-1-((2-chlorophenyl)(imino)methyl)cyclopentan-1-ol (4b). The NMR data matched those reported in the literature.[S4] **ESI HRMS** *m/z* $C_{12}H_{15}ClNO^+$ $[M+H]^+$: calcd 224.0836 ; found 224.0828.



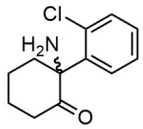
$C_{19}H_{20}ClNO$
MW 313.83

(±)-1-((benzylimino)(2-chlorophenyl)methyl)cyclopentan-1-ol (4c). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.48-7.07 (m, 9H), 5.61 (s, 1H), 4.30 (dd, *J* = 97.6, 15.6 Hz, 2H), 2.00-1.56 (m, 8H) ppm. **^{13}C NMR ($CDCl_3$, 100.6 MHz):** δ = 172.7, 139.4, 134.2, 132.1, 130.2, 130.0, 129.1, 128.4, 127.8, 126.9, 126.8, 84.5, 56.0, 38.7, 38.1, 23.7 ppm. **IR (neat)**: ν_{max} = 3287, 2962, 1644, 1409, 1355 cm^{-1}. **ESI HRMS** *m/z* $C_{19}H_{21}ClNO^+$ $[M+H]^+$: calcd 314.1306; found 314.1304.



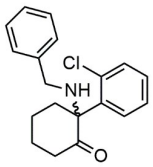
$C_{13}H_{16}ClNO$
MW 237.73

(±)-Ketamine (1a). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.55 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.38 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.32 (td, *J* = 7.7, 1.4 Hz, 1H), 7.24 (td, *J* = 7.5, 2.3 Hz, 1H), 2.85-2.72 (m, 1H), 2.56-2.42 (m, 2H), 2.11 (s, 3H), 2.07-1.68 (m, 5H) ppm. **^{13}C NMR ($CDCl_3$, 100.6 MHz):** δ = 209.3, 138.0, 133.9, 131.4, 129.5, 128.8, 126.7, 70.3, 39.7, 38.8, 29.3, 28.2, 22.0 ppm. The NMR data matched those reported in the literature.[S5] **IR (neat)**: ν_{max} = 3350, 2944, 2866, 2809, 1698 cm^{-1}. **ESI HRMS** *m/z* $C_{13}H_{17}ClNO^+$ $[M+H]^+$: calcd 238.0993; found 238.0994.



$C_{12}H_{14}ClNO$
MW 223.70

(±)-Norketamine (1b). The NMR data matched those reported in the literature.[S6] **ESI HRMS** *m/z* $C_{12}H_{15}ClNO^+$ $[M+H]^+$: calcd 224.0836 ; found 224.0834.



$C_{19}H_{20}ClNO$
MW 313.83

(±)-2-(benzylamino)-2-(2-chlorophenyl)cyclohexan-1-one (1c). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.67 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.43-7.21 (m, 8H), 3.42 (dd, *J* = 88.9, 13 Hz, 2H), 2.93 (s, 1H), 2.82-2.71 (m, 1H), 2.62-2.45 (m, 2H), 2.02-1.73 (m, 5H) ppm. **^{13}C NMR ($CDCl_3$, 100.6 MHz):** δ = 208.5, 140.0, 138.1, 133.8, 131.3, 129.4, 129.0, 128.5, 128.3, 127.2, 127.0, 70.2, 47.0, 39.6, 39.4, 27.7, 21.9 ppm. **IR (neat)**: ν_{max} = 2940, 2863, 1700, 1453, 1430 cm^{-1}. **ESI HRMS** *m/z* $C_{19}H_{21}ClNO^+$ $[M+H]^+$: calcd 314.1306; found 314.1306.

2.4 Structural identification of *N*-(2-chlorobenzylidene)methanamine (8)

The following NMR spectra have been collected at 400 MHz on a crude fraction of the reactor effluent (thermolysis of iminol **4a**).

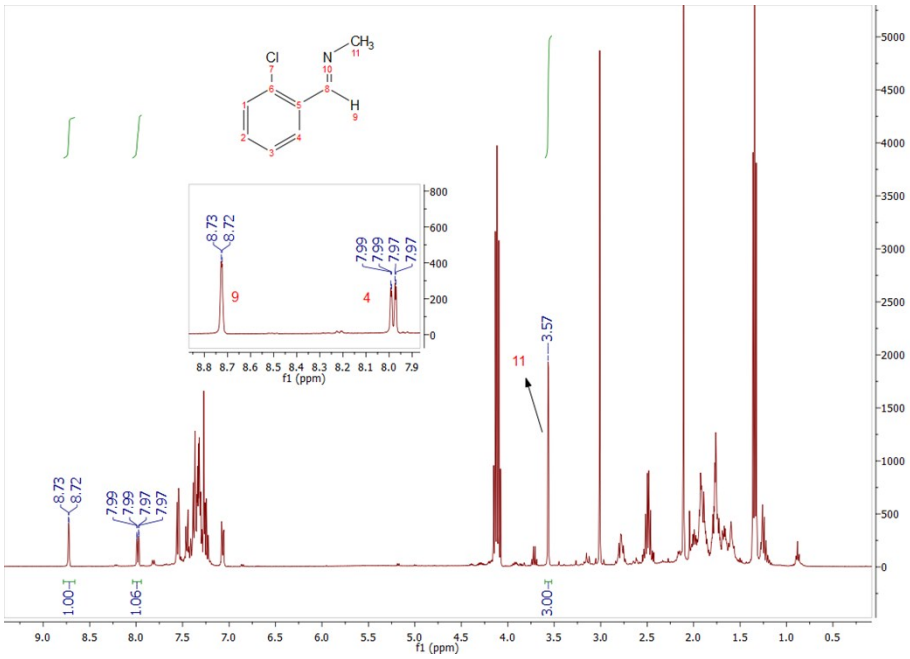


Figure S17. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of a crude effluent from the homogeneous thermolysis reactor. The peaks of *N*-(2-chlorobenzylidene)methanamine (**8**) are highlighted. The NMR data matched those reported in the literature.[S7]

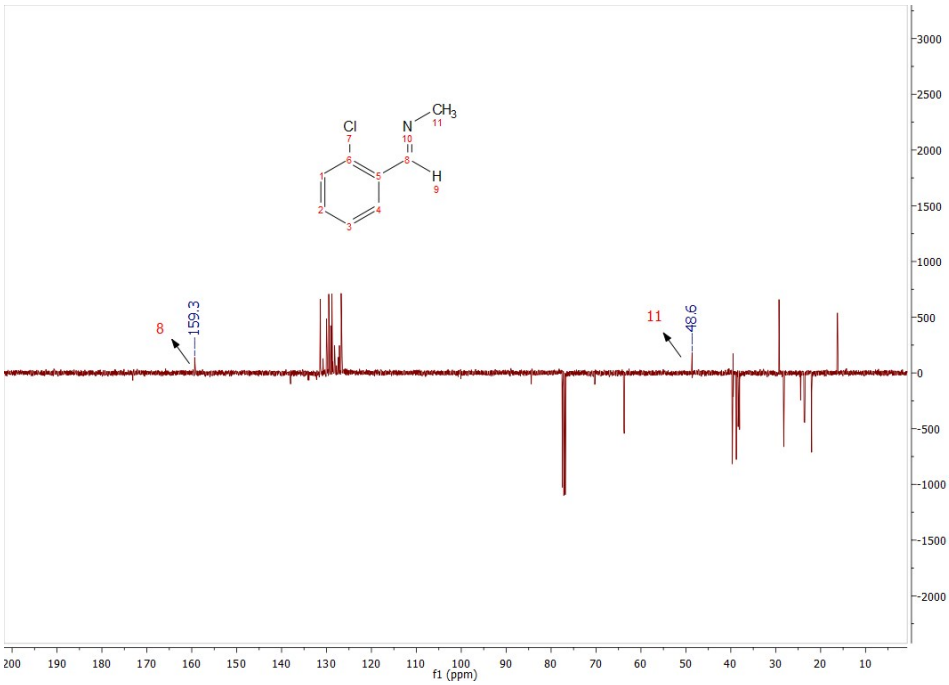


Figure S18. ^{13}C APT NMR spectrum (100.6 MHz, $CDCl_3$) of a crude effluent from the homogeneous thermolysis reactor. The peaks of *N*-(2-chlorobenzylidene)methanamine (**8**) are highlighted. The NMR data matched those reported in the literature.[S7]

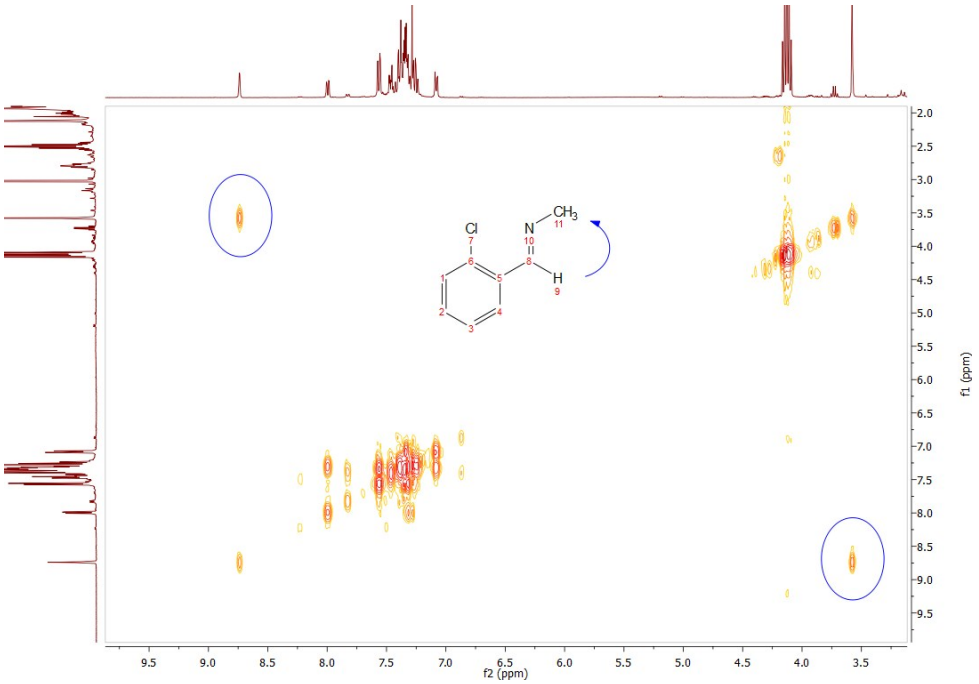


Figure S19. COSY NMR spectrum ($CDCl_3$) of a crude effluent from the homogeneous thermolysis reactor. The interaction between representative peaks of *N*-(2-chlorobenzylidene)methanamine (**8**) are highlighted.

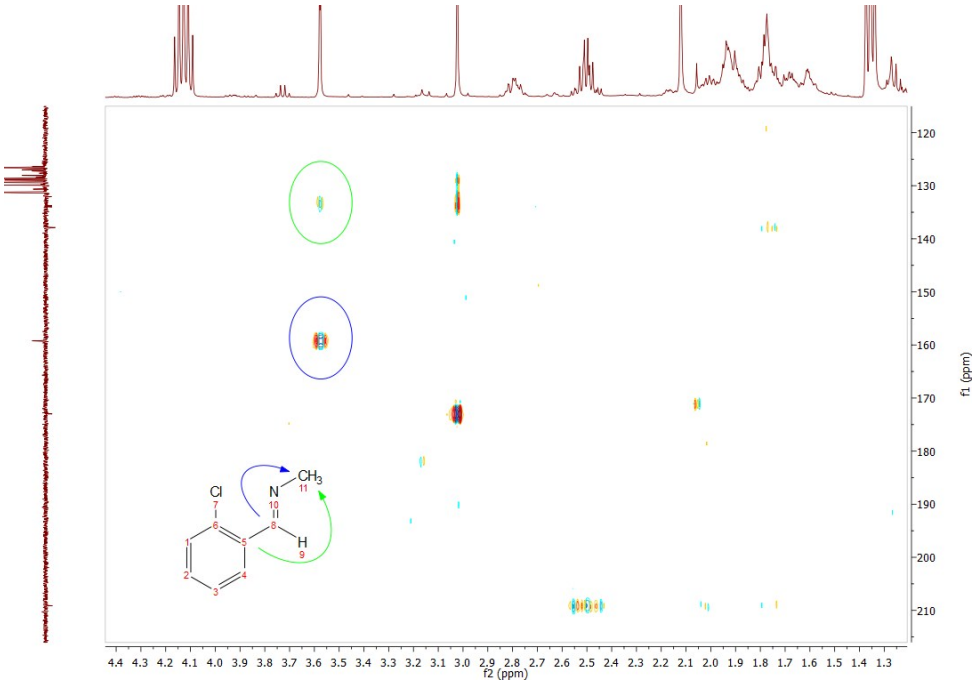


Figure S20. HMBC NMR spectrum ($CDCl_3$) of a crude effluent from the homogeneous thermolysis reactor. The interactions between representative peaks of *N*-(2-chlorobenzylidene)methanamine (**8**) are highlighted.

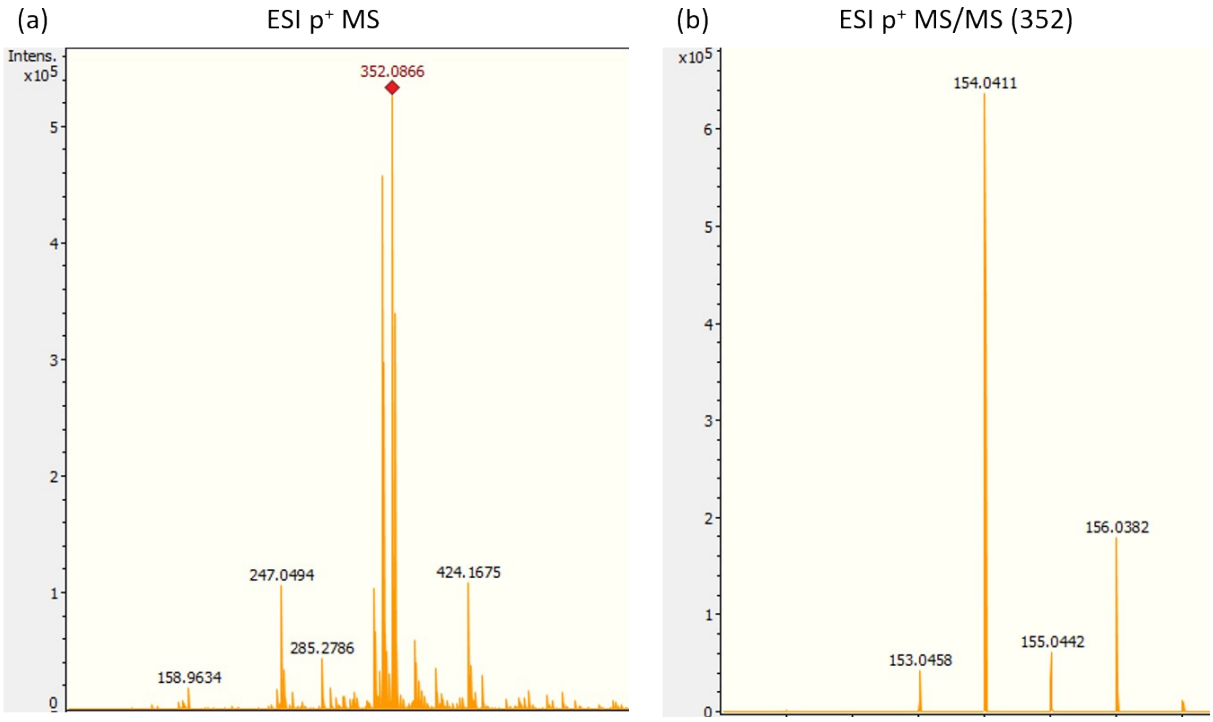


Figure S21. MS analysis of *N*-(2-chlorobenzylidene)methanamine (**8**). The material was isolated from a crude effluent from the homogeneous thermolysis reactor by micropreparative HPLC/DAD. ESI HRMS/MS (352) *m/z* $C_8H_9ClN^+$ $[M+H]^+$: calcd 154.0423; found 154.0411.

2.5 LC analysis of key intermediates

2.5.1 Analytical Method

Eluent: A: Water + 0.1% CF_3COOH (v:v)
B: Acetonitrile

Gradient Table:

Time [min]	A [%]	B [%]
0	100	0
20	20	80
23	20	80
25	100	0
31	100	0

Flow: 1 $mL.min^{-1}$
Injection Volume: 10-20 µL
Column: C18, 100 × 4.6 mm, 3 µm
Oven Temperature: 40 °C
Diode Array Detector: 180-800 nm (processed either at 216 nm [imination and thermolysis) or at 220 nm (hydroxylation)]

2.5.2 Copies of LC traces

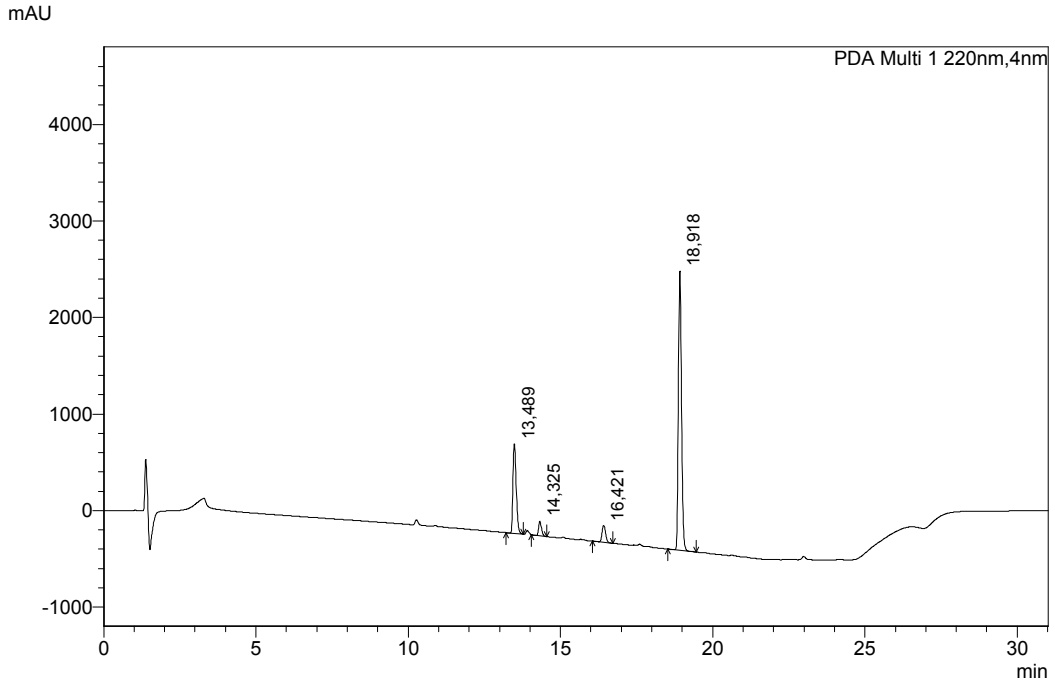


Figure S22. LC trace of crude (±)-(2-chlorophenyl)(1-hydroxycyclopentyl)methanone (**7**) after hydroxylation using EtOLi as base (Entry 1, Table S6). Peak identification was conducted using purified substances analyzed by either NMR and/or HRMS. Peak #1 (13.48 min) = compound **iso-7**, peak #2 (14.32 min) = compound **7**, peak #3 (16.42 min) = unidentified compound and peak #4 (18.91 min) = compound **2**.

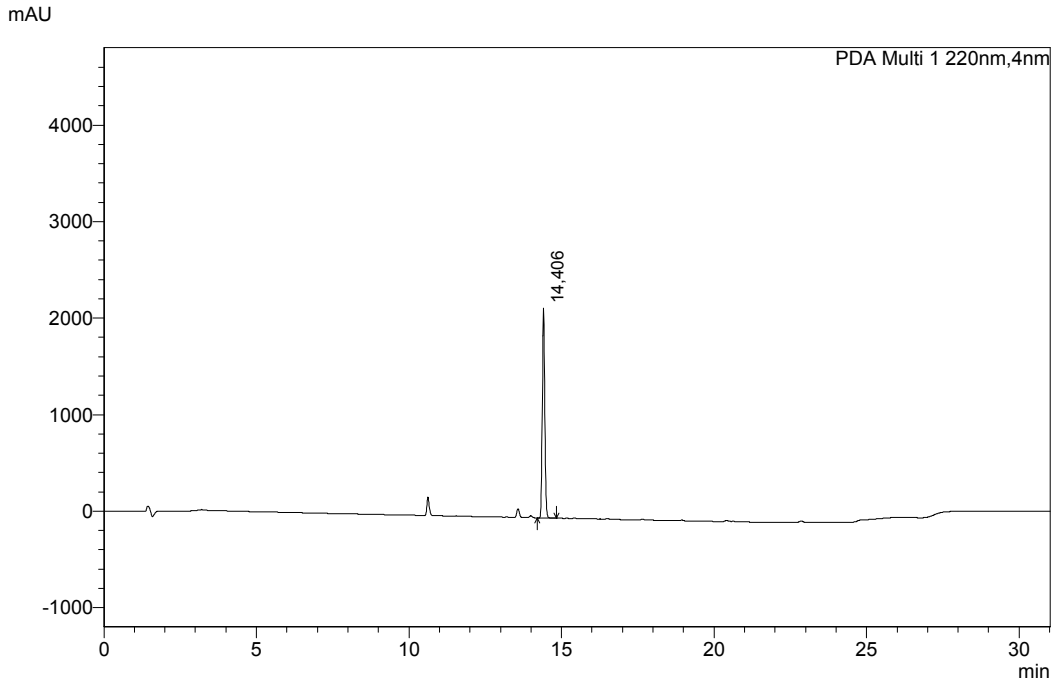


Figure S23. LC trace of crude (±)-(2-chlorophenyl)(1-hydroxycyclopentyl)methanone (**7**) after hydroxylation using KOH as base (Entry 6, Table S9). Peak identification was conducted using purified substances analyzed by either NMR and/or HRMS. Peak #1 (14.40 min) = compound **7.**

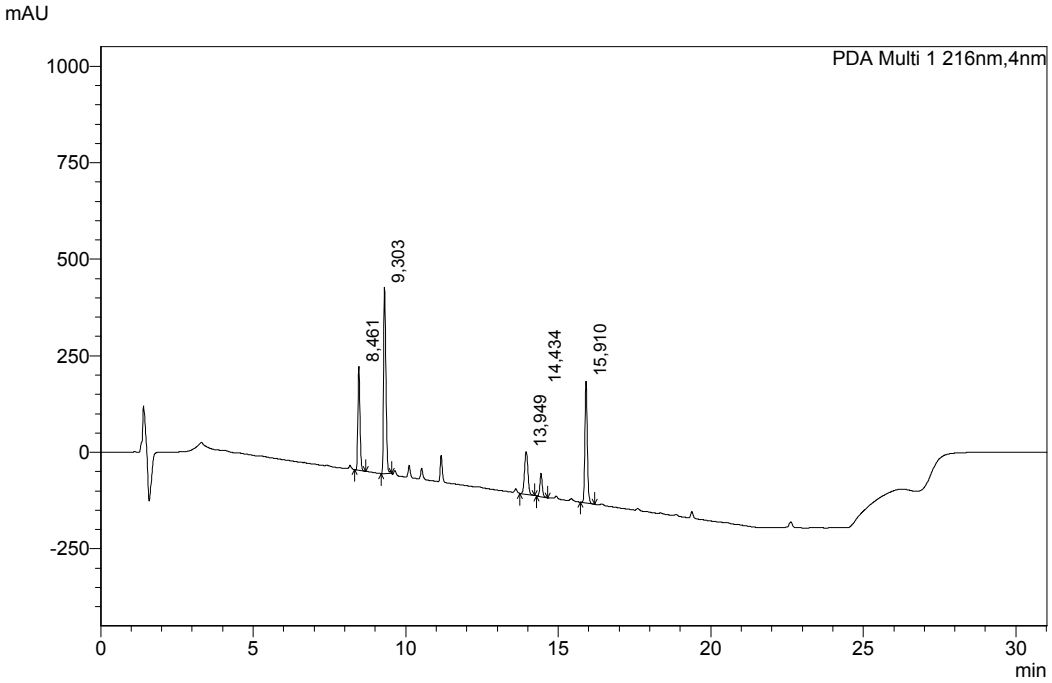


Figure S24. LC trace of crude (±)-1-((2-chlorophenyl)(methylimino)methyl)cyclopentan-1-ol (**4a**) after imination for 10 min at 180 °C without Lewis acid (see Figure S14). Peak identification was conducted using purified substances analyzed by either NMR and/or HRMS. Peak #1 (8.46 min) = compound **1a**, peak #2 (9.30 min) = compound **4a**, peak #3 (13.94 min) = compound **8**, peak #4 (14.34 min) = compound **7** and peak #5 (15.91 min) = compound **9**.

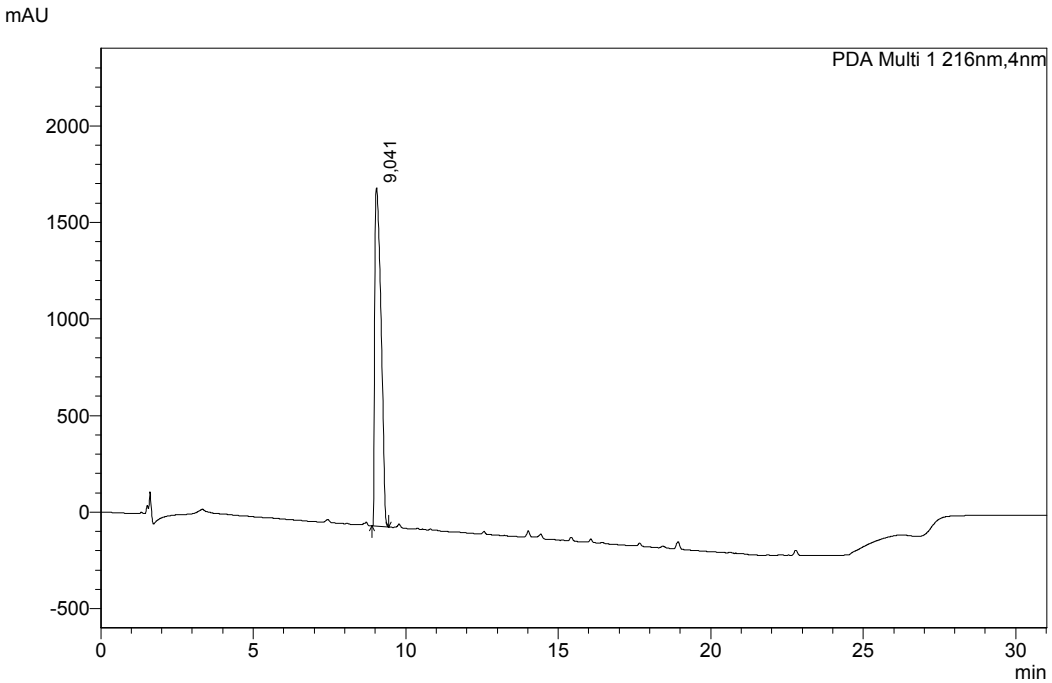


Figure S25. LC trace of crude (±)-1-((2-chlorophenyl)(methylimino)methyl)cyclopentan-1-ol (**4a**) after imination using $B(O^iPr)_3$ as Lewis acid (Entry 4, Table 3). Peak identification was conducted using purified substances analyzed by either NMR and/or HRMS. Peak #1 (9.04 min) = compound **4a**.

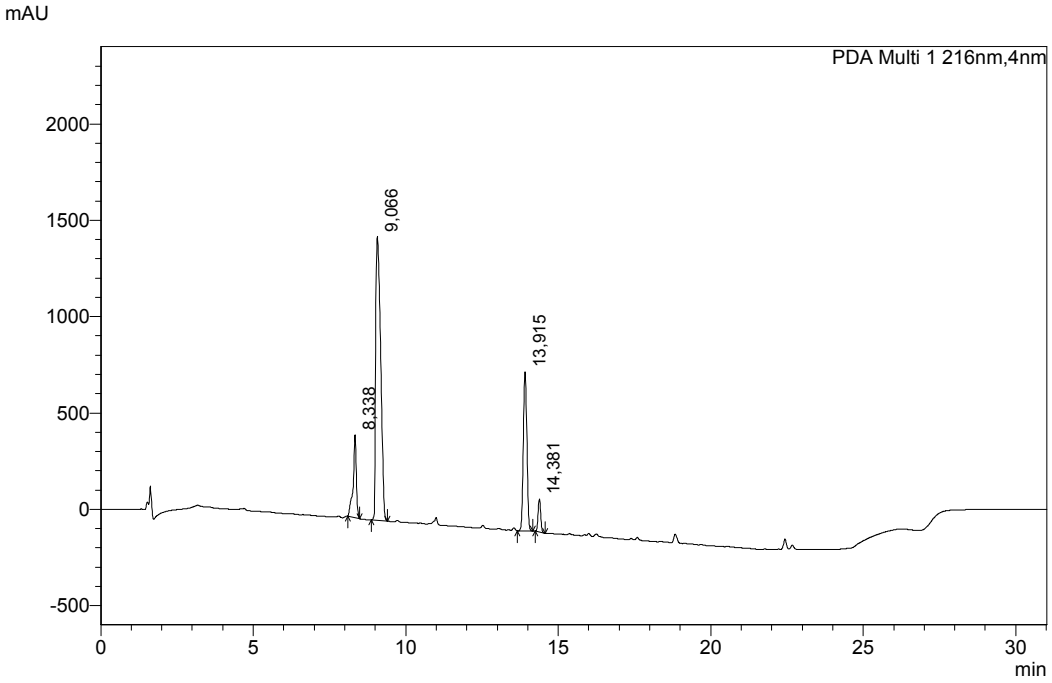


Figure S26. LC trace of crude (±)-ketamine (**1a**) after thermolysis without heterogeneous catalyst in MeTHF at 240 °C (Entry 17, Table 4). Peak identification was conducted using purified substances analyzed by either NMR and/or HRMS. Peak #1 (8.33 min) = compound **1a**, peak #2 (9.06 min) = compound **4a**, peak #3 (13.91 min) = compound **8** and peak #4 (14.38 min) = compound **7**.

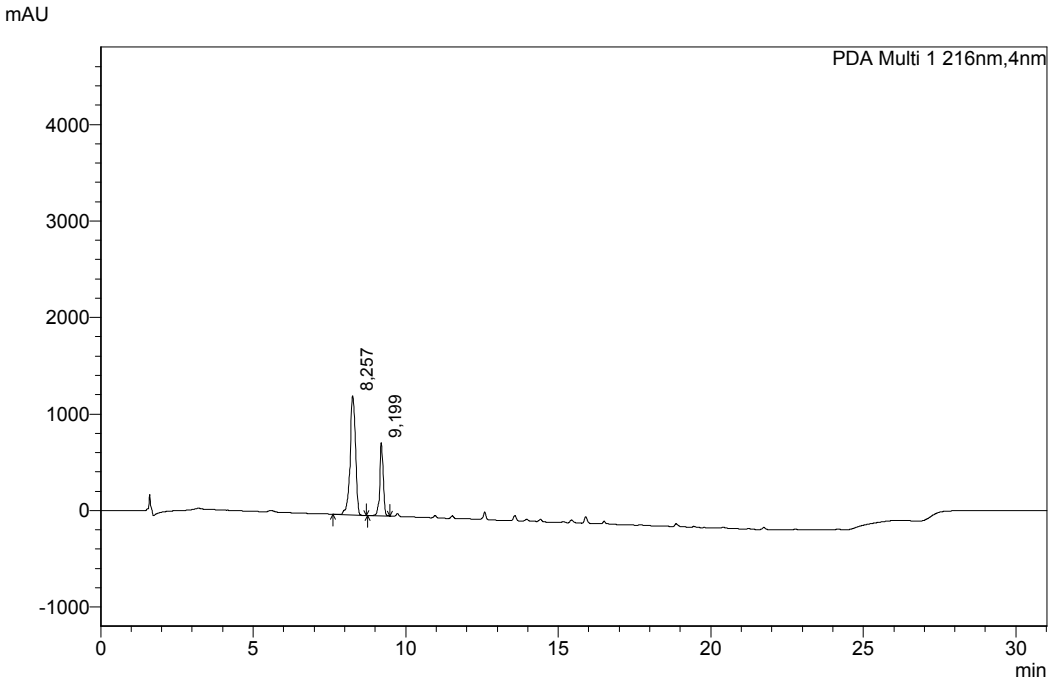


Figure S27. LC trace of crude (±)-ketamine (**1a**) after thermolysis using K10 as heterogeneous catalyst in ethanol at 180 °C (Entry 1, Table 6). Peak identification was conducted using purified substances analyzed by either NMR and/or HRMS. Peak #1 (8.25 min) = compound **1a** and peak #2 (9.19 min) = compound **4a**.

2.6 Copies of ^{1}H and ^{13}C NMR spectra

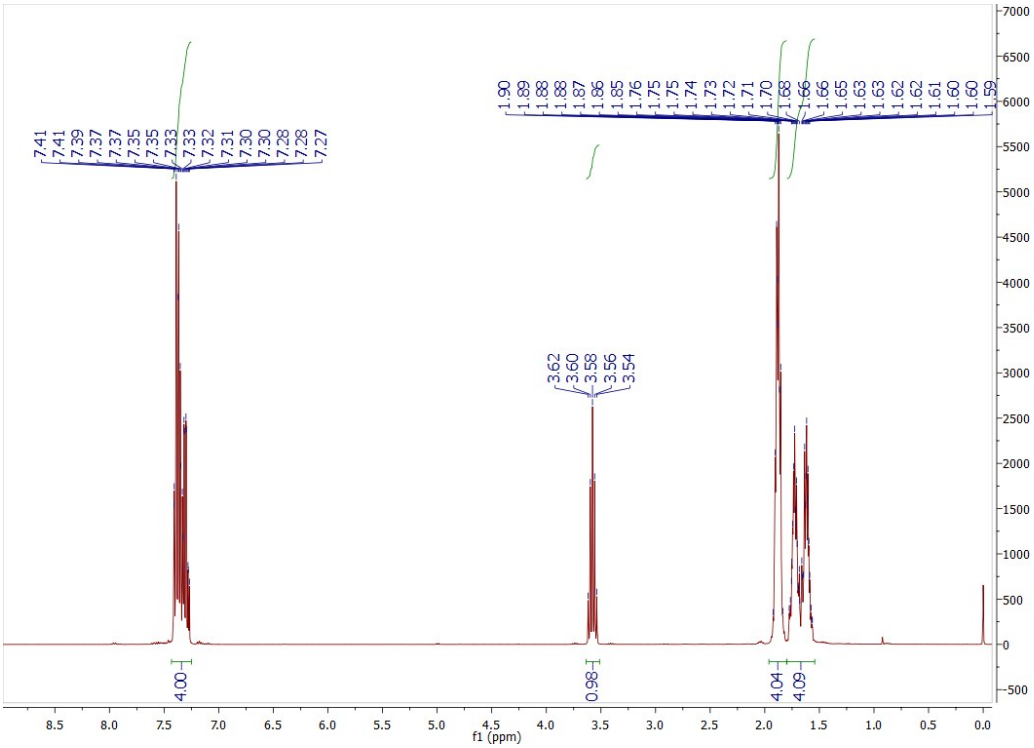


Figure S28. ^{1}H NMR spectrum (400 MHz) of (2-chlorophenyl)(cyclopentyl)methanone (**2**) in $CDCl_3$.

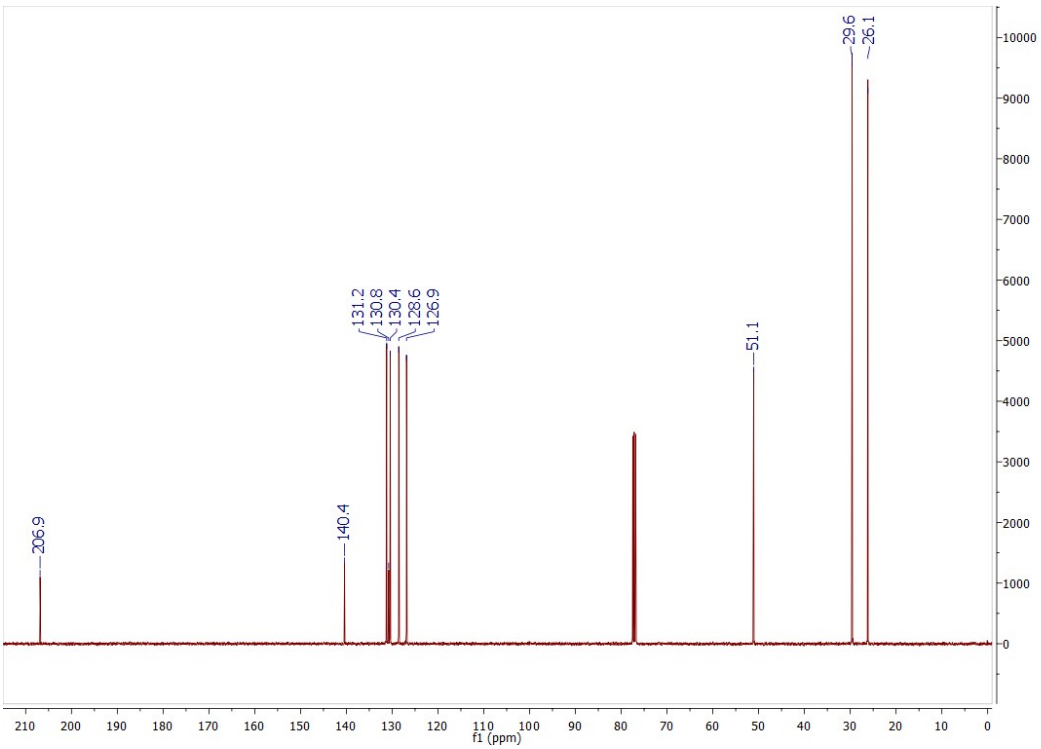


Figure S29. ^{13}C NMR spectrum (100.6 MHz) of (2-chlorophenyl)(cyclopentyl)methanone (**2**) in $CDCl_3$.

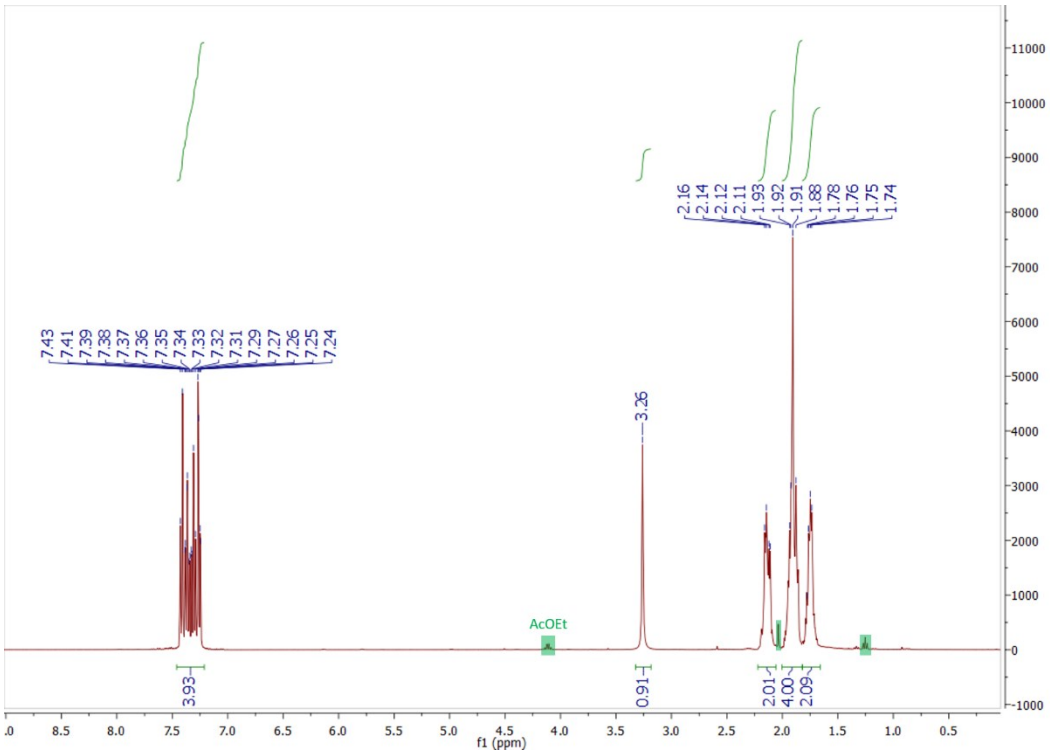


Figure S30. ^{1}H NMR spectrum (400 MHz) of (±)-(2-chlorophenyl)(1-hydroxycyclopentyl)methanone (**7**) in $CDCl_3$.

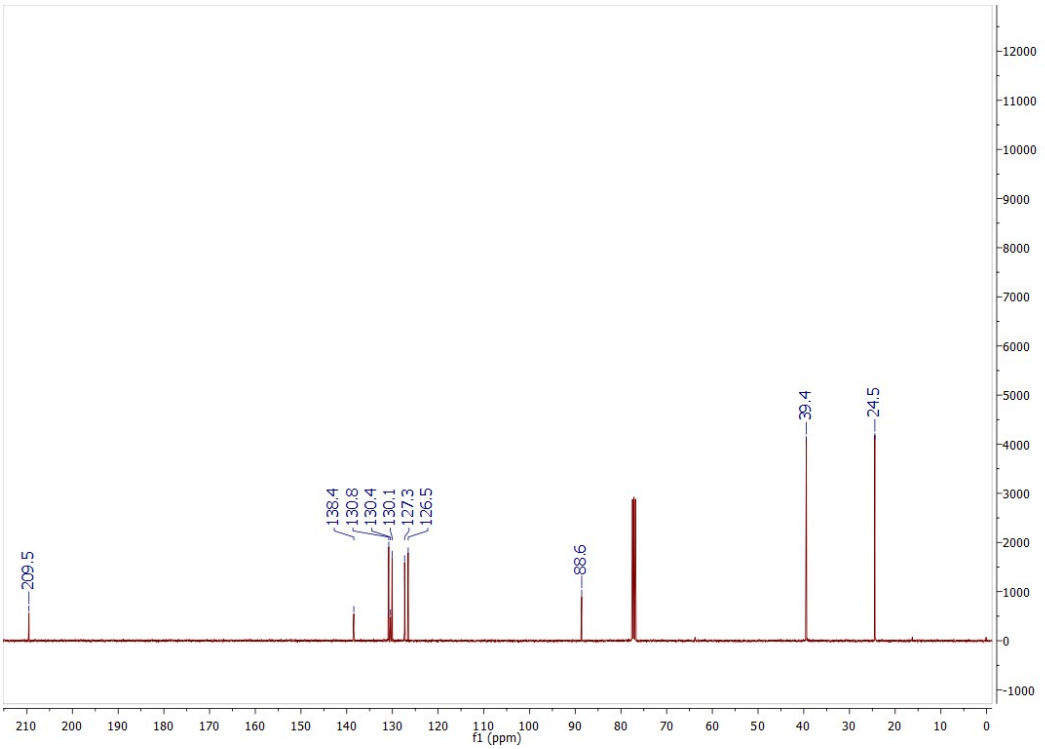


Figure S31. ^{13}C NMR spectrum (100.6 MHz) of (±)-(2-chlorophenyl)(1-hydroxycyclopentyl)methanone (**7**) in $CDCl_3$.

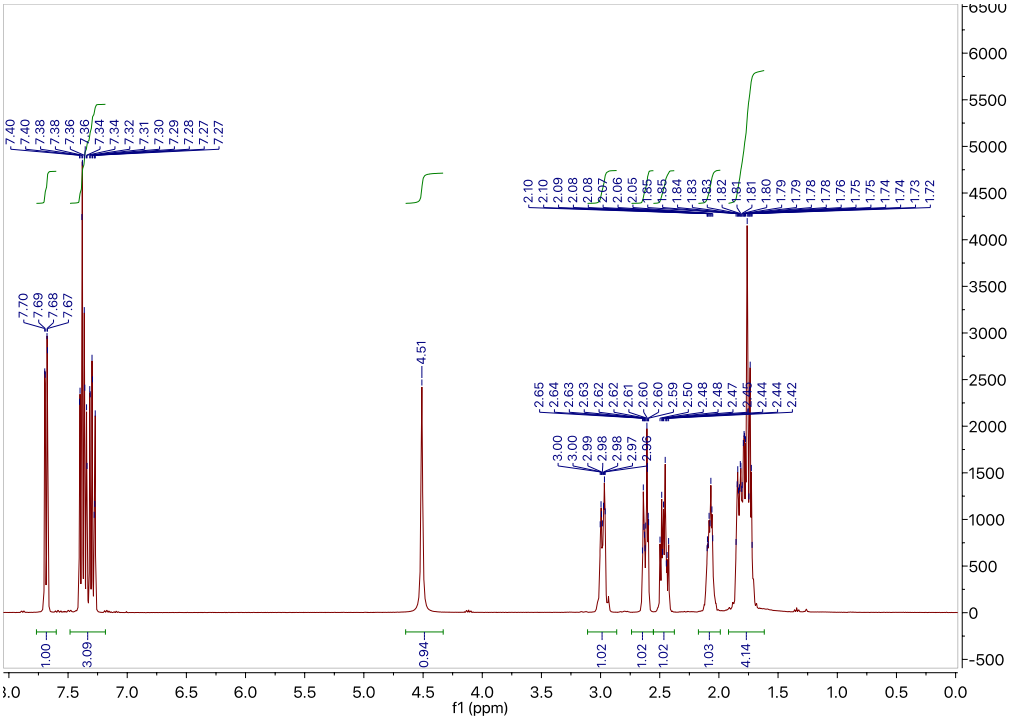


Figure S32. ^{1}H NMR spectrum (400 MHz) of (±)-2-(2-chlorophenyl)-2-hydroxycyclohexan-1-one (**iso-7**) in $CDCl_3$.

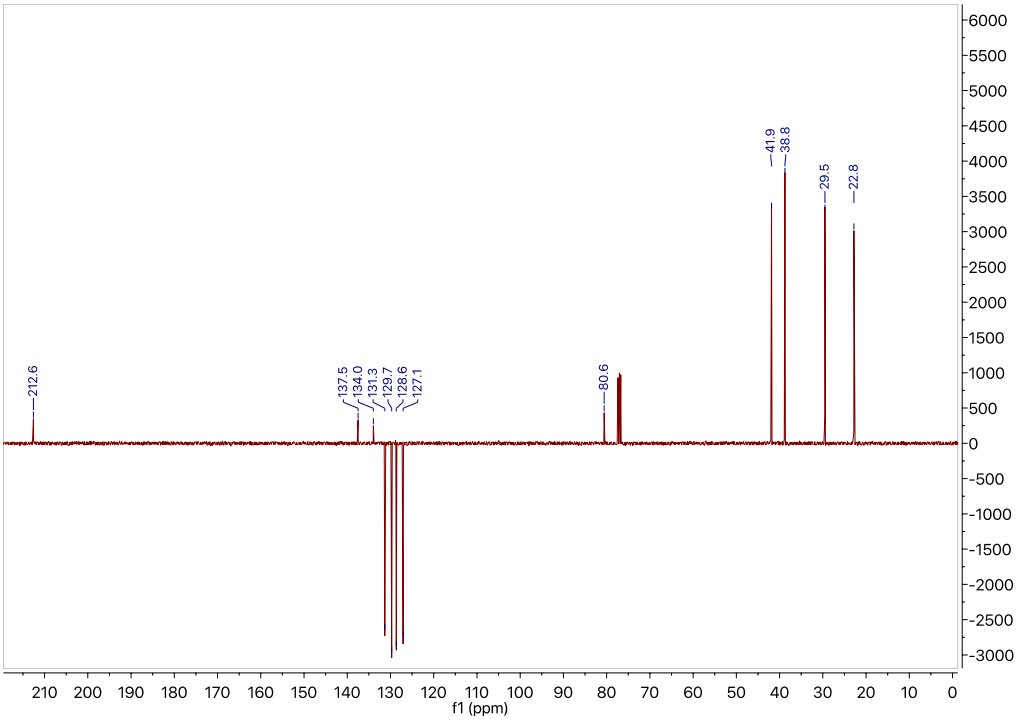


Figure S33. ^{13}C APT NMR spectrum (100.6 MHz) of ((±)-2-(2-chlorophenyl)-2-hydroxycyclohexan-1-one (**iso-7**) in $CDCl_3$.

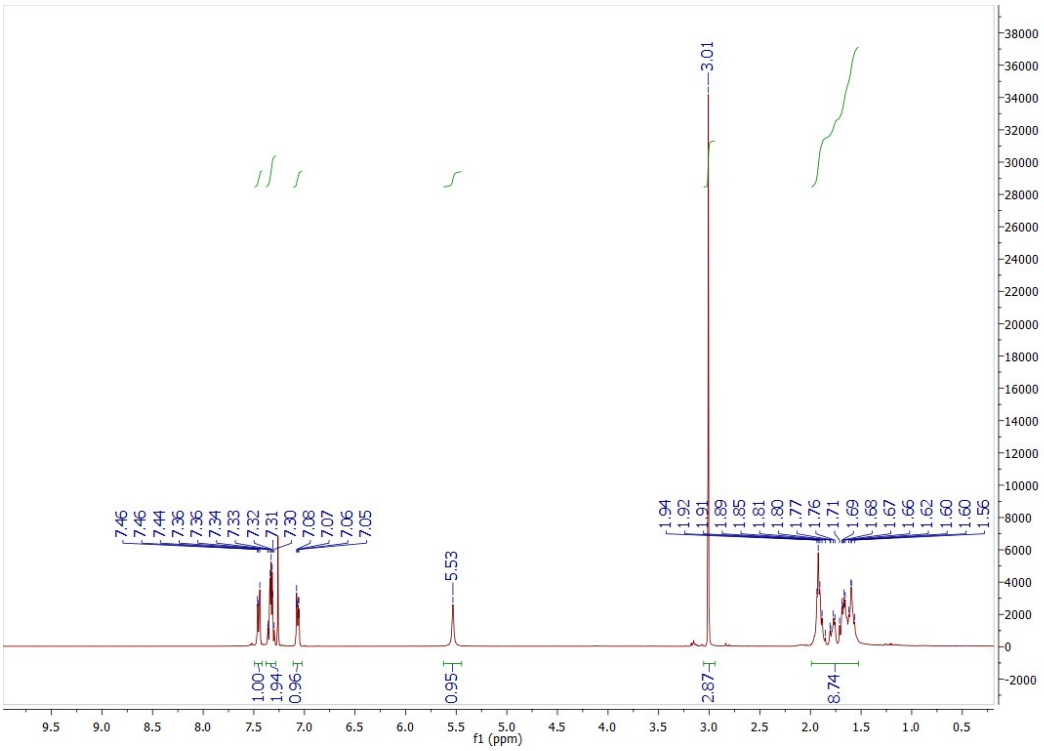


Figure S34. ^{1}H NMR spectrum (400 MHz) of (±)-1-((2-chlorophenyl)(methylimino)methyl)cyclopentan-1-ol (**4a**) in $CDCl_3$.

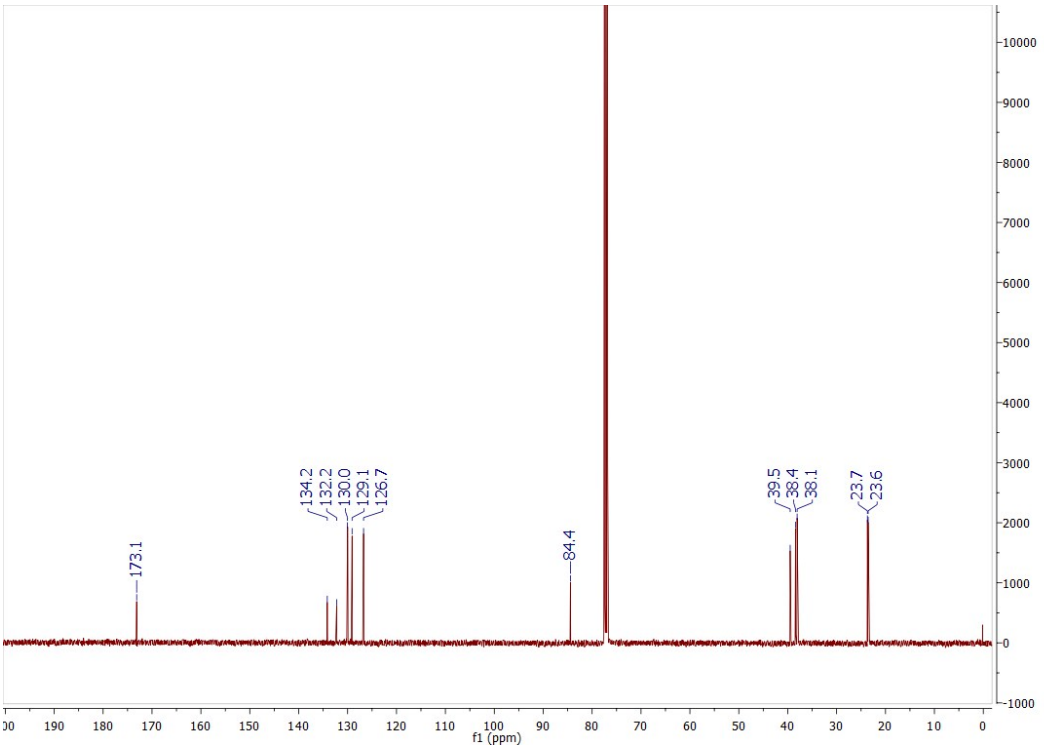


Figure S35. ^{13}C NMR spectrum (100.6 MHz) of (±)-1-((2-chlorophenyl)(methylimino)methyl)cyclopentan-1-ol (**4a**) in $CDCl_3$.

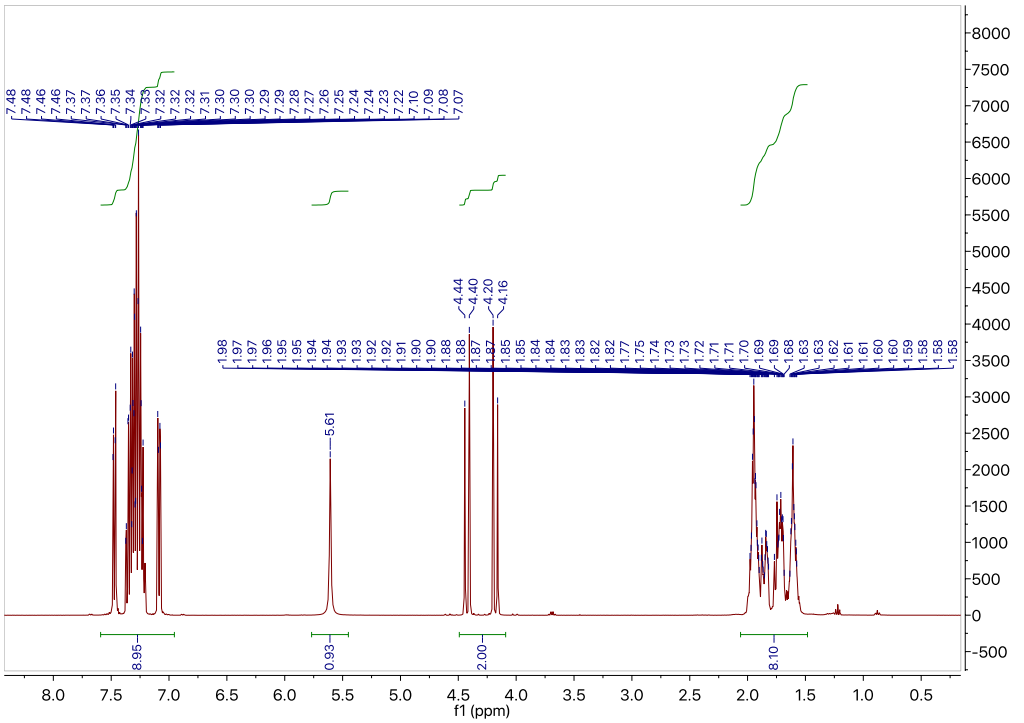


Figure S36. ^{1}H NMR spectrum (400 MHz) of (±)-1-((benzylimino)(2-chlorophenyl)methyl)cyclopentan-1-ol (**4c**) in $CDCl_3$.

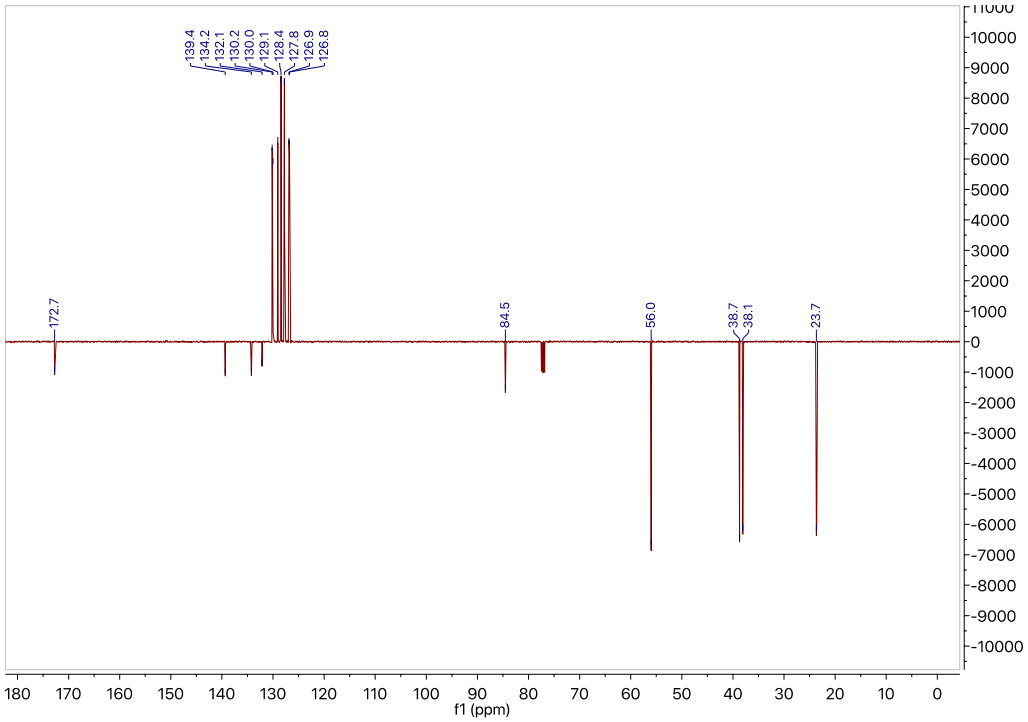


Figure S37. ^{13}C APT NMR spectrum (100.6 MHz) of (±)-1-((benzylimino)(2-chlorophenyl)methyl)cyclopentan-1-ol (**4c**) in $CDCl_3$.

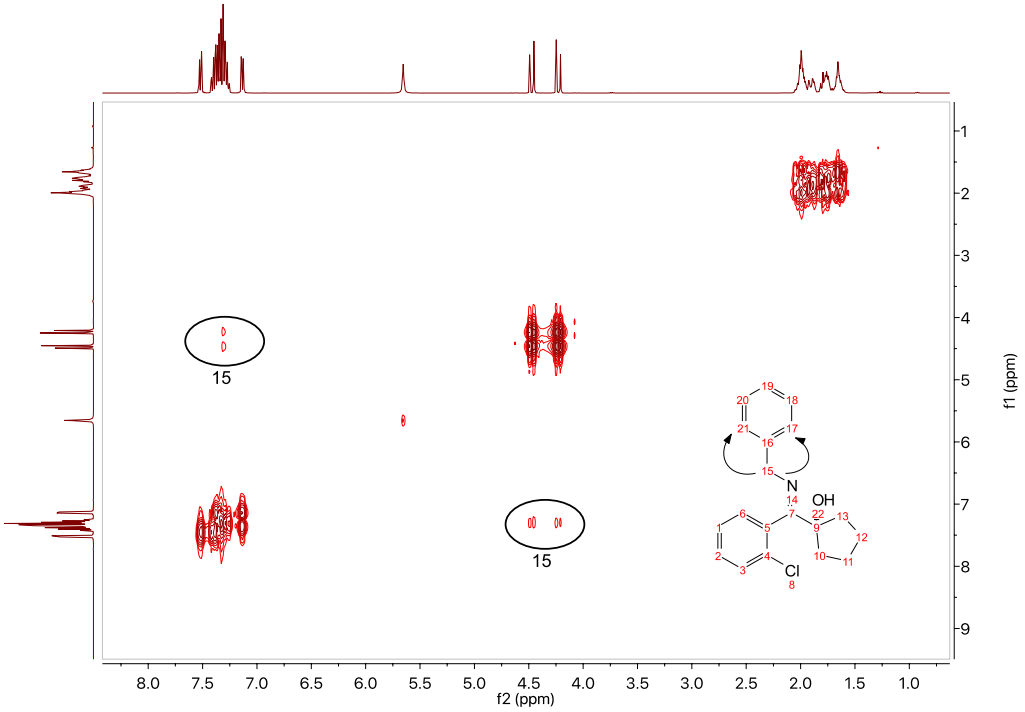


Figure S38. ^{1}H COSY NMR spectrum of (±)-1-((benzylimino)(2-chlorophenyl)methyl)cyclopentan-1-ol (**4c**) in $CDCl_3$.

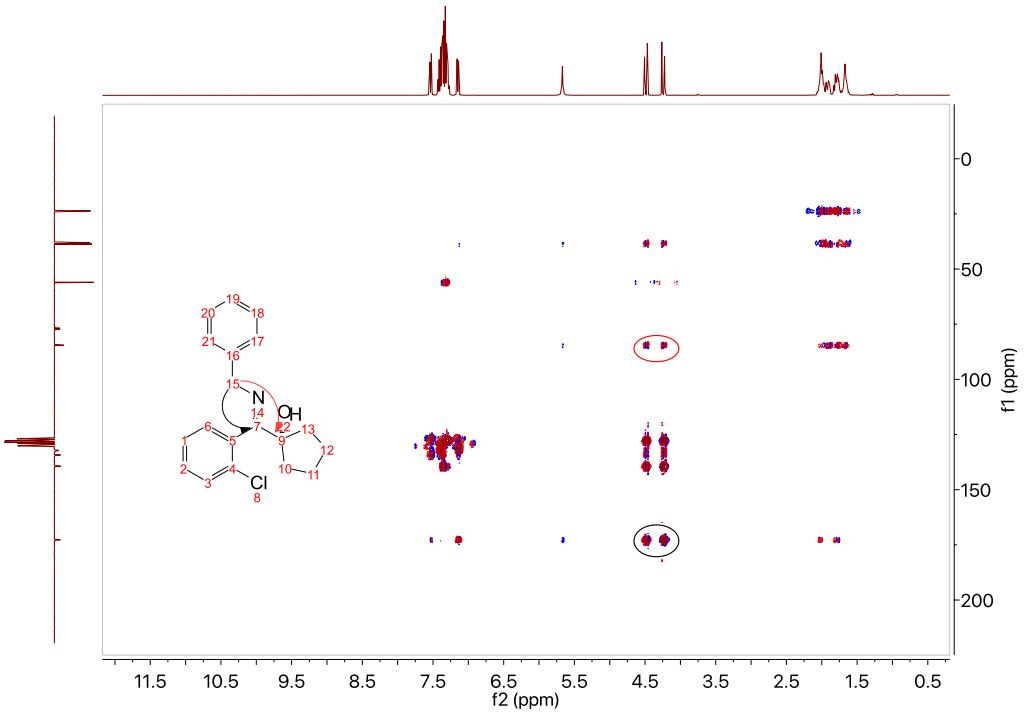


Figure S39. HMBC NMR spectrum of (±)-1-((benzylimino)(2-chlorophenyl)methyl)cyclopentan-1-ol (**4c**) in $CDCl_3$.

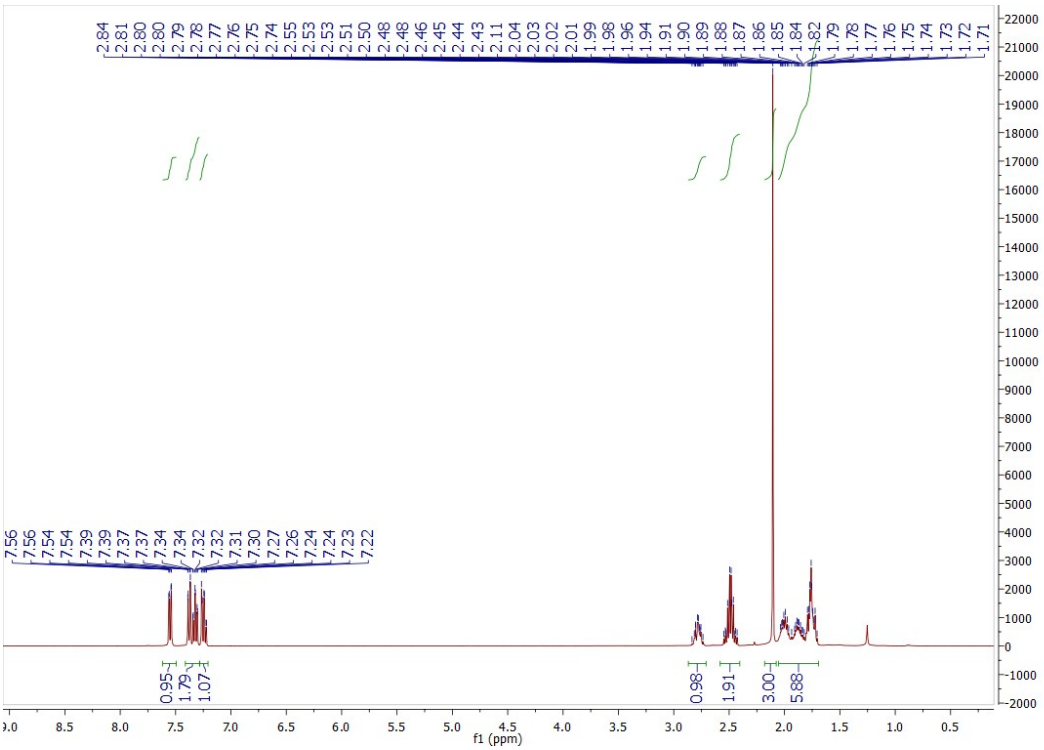


Figure S40. ^{1}H NMR spectrum (400 MHz) of (±)-ketamine (**1a**) in $CDCl_3$.

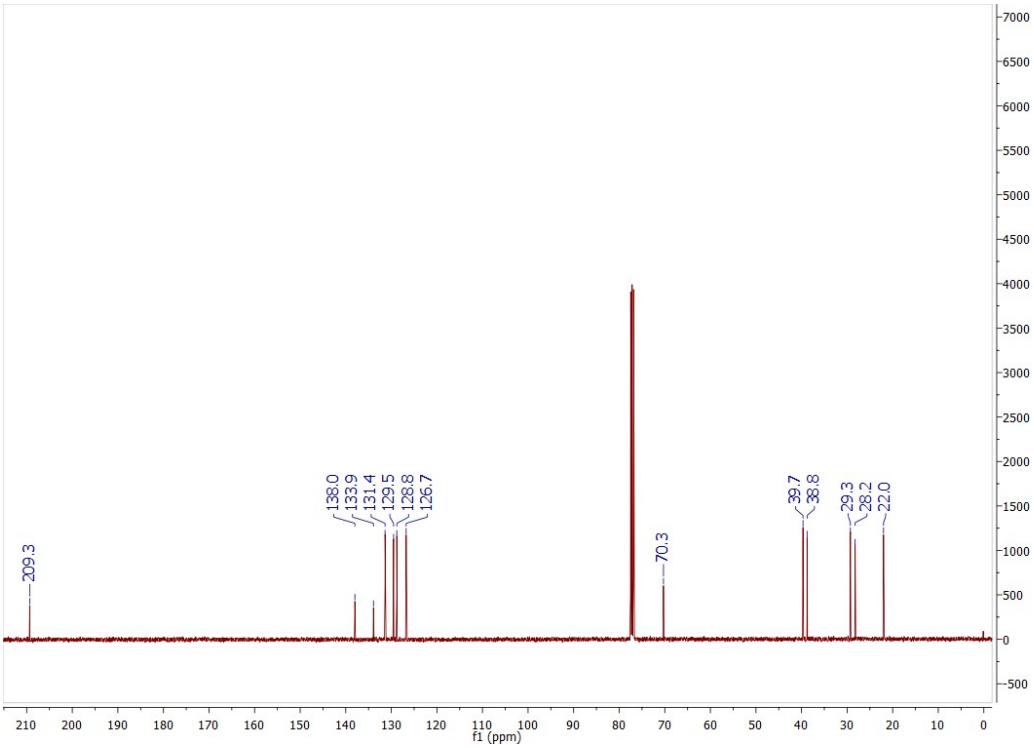


Figure S41. ^{13}C NMR spectrum (100.6 MHz) of (±)-ketamine (**1a**) in $CDCl_3$.

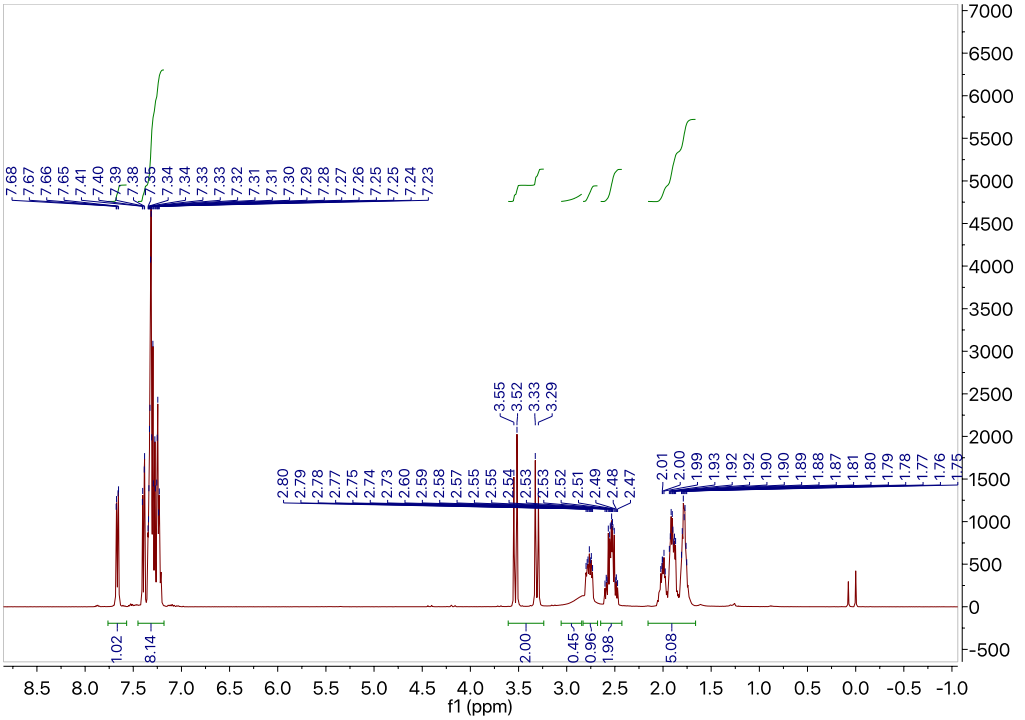


Figure S42. ^{1}H NMR spectrum (400 MHz) of (±)-2-(benzylamino)-2-(2-chlorophenyl)cyclohexan-1-one ((±)-**1c**) in $CDCl_3$

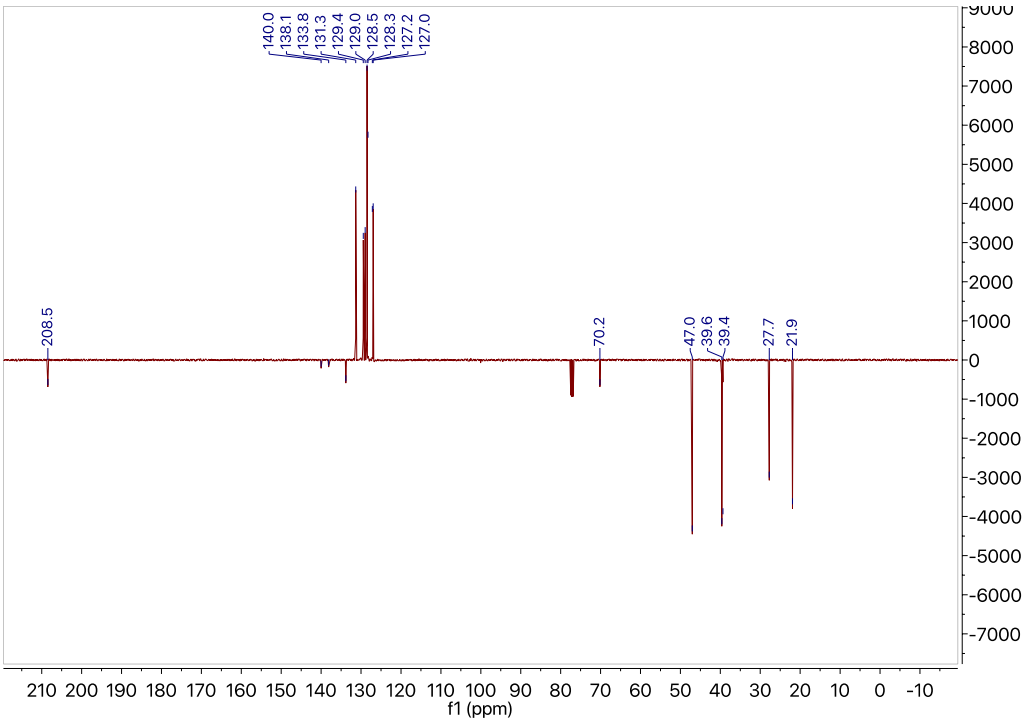


Figure S43. ^{13}C APT NMR spectrum (100.6 MHz) of (±)-2-(benzylamino)-2-(2-chlorophenyl)cyclohexan-1-one ((±)-**1c**) in $CDCl_3$.

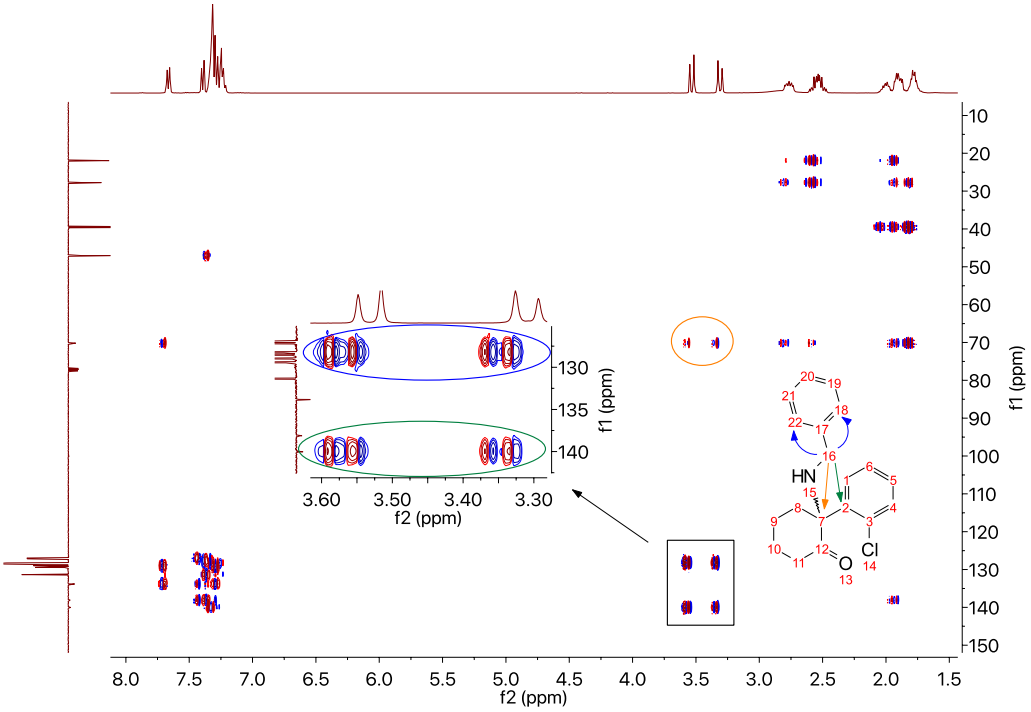


Figure S44. HMBC NMR spectrum of (±)-2-(benzylamino)-2-(2-chlorophenyl)cyclohexan-1-one ((±)-**1c**) in $CDCl_3$.

2.7 Copies of IR spectra for compounds 4c and (±)-1c

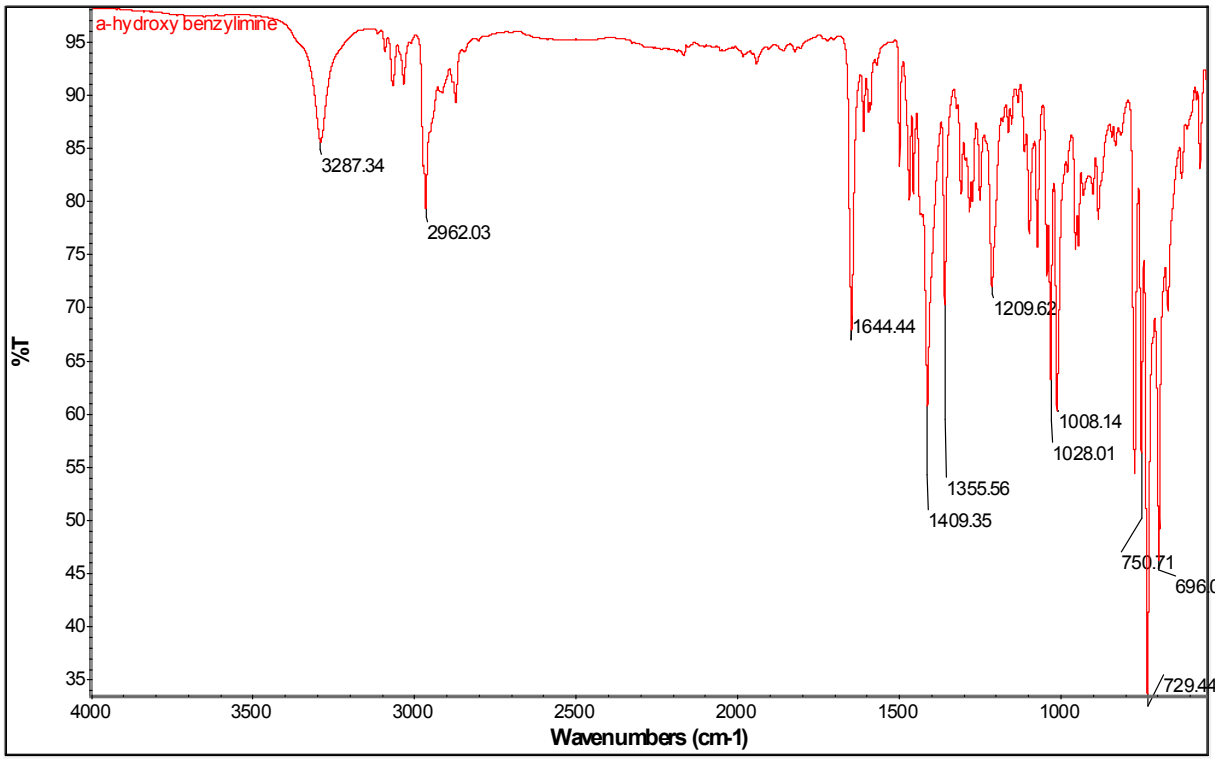


Figure S45. Infrared spectrum of (±)-1-((benzylimino)(2-chlorophenyl)methyl)cyclopentan-1-ol (neat) (**4c**).

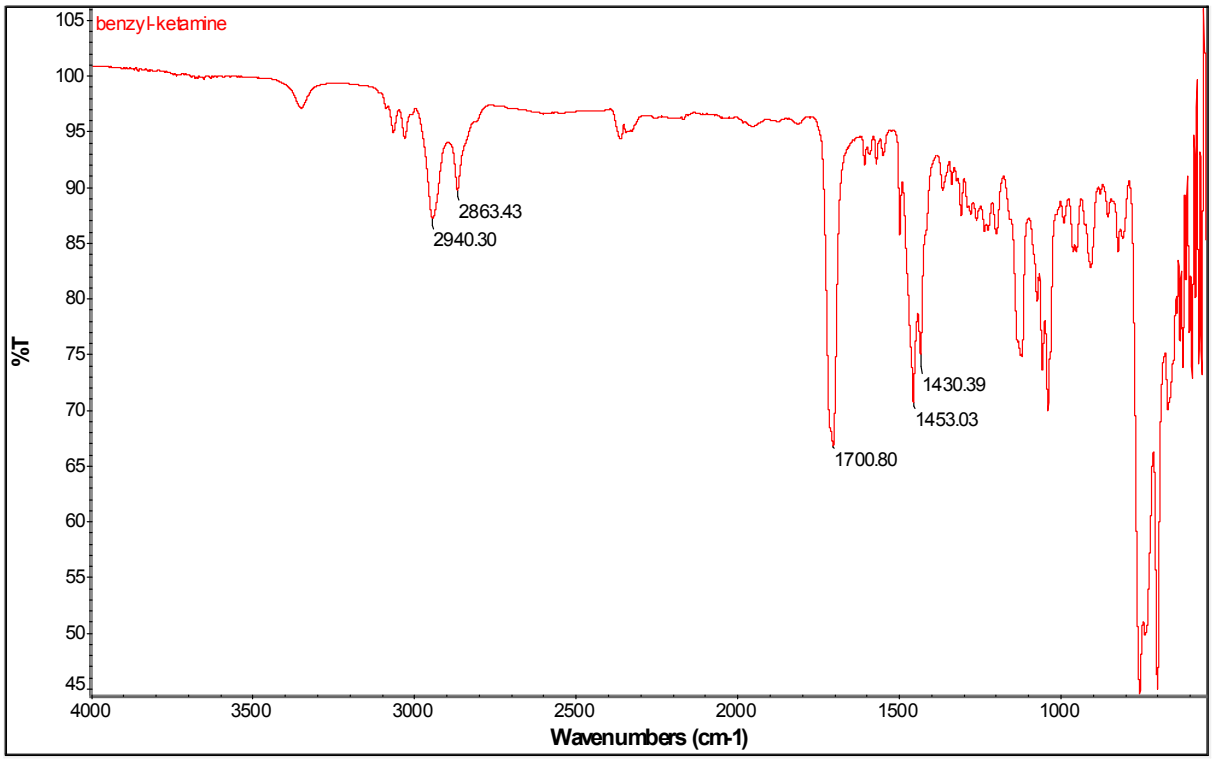


Figure S46. Infrared spectrum of (±)-2-(benzylamino)-2-(2-chlorophenyl)cyclohexan-1-one (neat) ((±)-**1c**).

2.8 Molecular structure by single crystal X-ray diffraction analysis of compounds iso-7, 4a and 1a

2.8.1 General information

Crystals of **iso-7**, **4a** and **1a** were obtained from the recrystallization of purified samples from hot solution in heptane or heptane/ethanol.

For the structures of **iso-7**, **4a** and **1a**, X-ray intensity data were collected at 100 K, on a Rigaku Oxford Diffraction Supernova Dual Source (Cu at zero) diffractometer equipped with an Atlas CCD detector using ω scans and CuKα (λ = 1.54184 Å) radiation. The images were interpreted and integrated with the program CrysAlisPro.[S8] Using Olex2,[S9] the structure was solved by direct methods using the ShelXS structure solution program and refined by full-matrix least-squares on F^2 using the ShelXL program package.[S10,11] Non-hydrogen atoms were anisotropically refined and the hydrogen atoms in the riding mode and isotropic temperature factors fixed at 1.2 times U(eq) of the parent atoms (1.5 times for methyl groups). O-H and N-H hydrogen atoms were located from a difference Fourier electron-density map and refined (restrained with an O-H distance of 0.84 Å, and unrestrained for **4a** and **1a**).

For **iso-7**, the absolute configuration was determined, with chirality at C7 (*R*), showing a refined Flack parameter of 0.057(13).

For **1a**, the asymmetric unit contains two different molecules, i.e. the first molecule has chirality at C7 (*R*) and the second molecule has chirality at C20 (*S*), hence the compound crystallized as a racemate. Also, the centro-symmetric space group $P2_1/c$, obviously implies the presence of both configurations.

2.8.2 Crystal data for compounds iso-**7**, **4a** and **1a**

CCDC 1893725-1893727 contain the supplementary crystallographic data for this paper and can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; or deposit@ccdc.cam.ac.uk).

2.8.2.1 Crystal data for compound **iso-7**.

$C_{12}H_{13}ClO_2$, M = 224.67, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 7.1261(4) Å, b = 8.1012(6) Å, c = 18.5115(9) Å, V = 1068.67(11) Å^3, Z = 4, T = 100 K, ρ_{calc} = 1.396 g cm^{-3}, μ(Cu-Kα) = 2.970 mm^{-1}, F(000) = 472, 4864 reflections measured, 2045 unique (R_{int} = 0.0390) which were used in all calculations. The final $R1$ was 0.0340 ($I > 2\sigma(I)$) and $wR2$ was 0.0882 (all data).

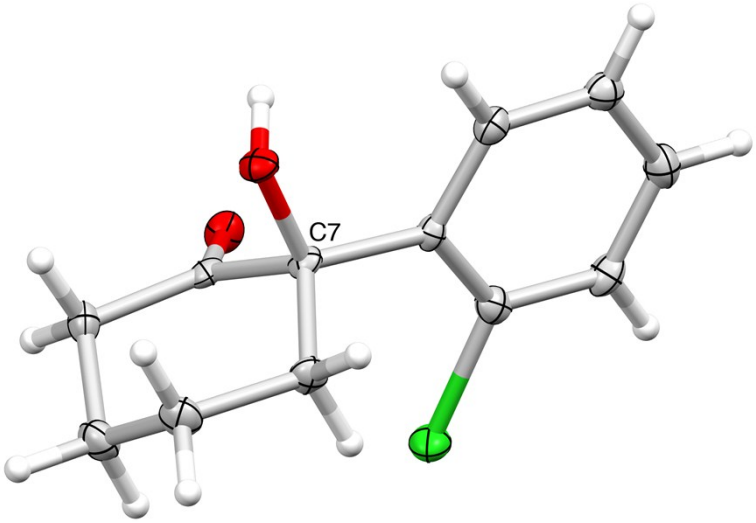


Figure S47. Asymmetric unit of the crystal structure of **iso-7**, showing thermal displacement ellipsoids at the 50% probability level. The chiral C7 (*R*) is labeled.

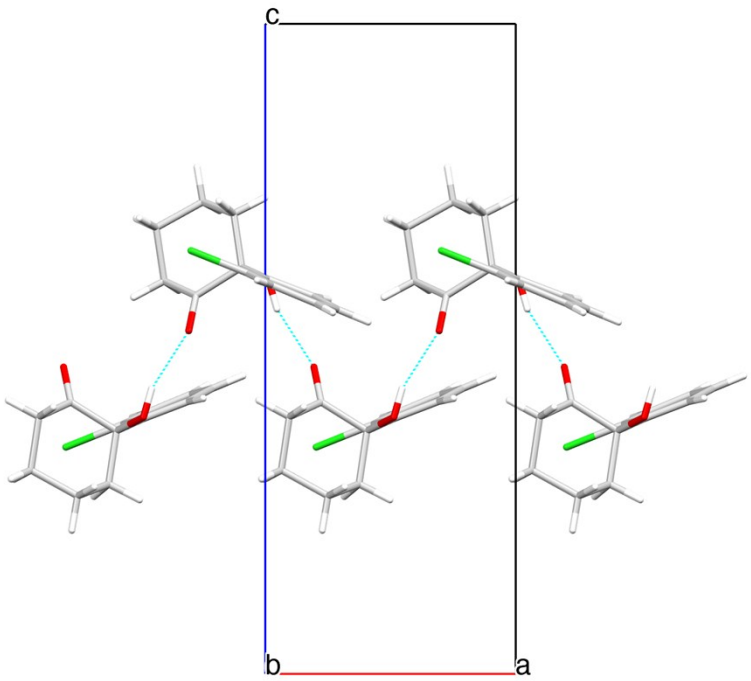


Figure S48. Hydrogen bonds formed between O-H and C=O functional groups in the crystal structure of **iso-7**, forming chains along the [100] direction.

Note: There is no reason to assume that the formation of **iso-7** is enantioselective given the conditions utilized. The starting compound **2** is achiral, and no source of chirality was used during the reaction and the crystallization of **iso-7** prior to structure determination by single crystal X-ray diffraction analysis. The X-ray diffraction analysis does confirm the (*R*)-configuration on the stereogenic carbon, thus emphasizing that a single stereoisomer was obtained through the crystallization process. Axial chirality of the Cl-Ph group could contribute to the formation of diastereomeric species upon crystallization, hence potentially leading to stereo enrichment of the crystals. Such a specific phenomenon was recently reported in the literature by Gataullin and coworkers.[S12] For further information, see also Section 3.6.

2.8.2.2 Crystal data for compound **4a**.

$C_{13}H_{16}ClNO$, M = 237.72, triclinic, space group P-1 (No. 2), a = 6.7087(3) Å, b = 8.9522(3) Å, c = 10.8050(4) Å, α = 76.216(3)°, β = 82.767(3)°, γ = 72.956(3)°, V = 601.46(4) Å^3, Z = 2, T = 100 K, ρ_{calc} = 1.313 g cm^{-3}, μ(Cu-Kα) = 2.626 mm^{-1}, F(000) = 252, 14432 reflections measured, 2437 unique (R_{int} = 0.0482) which were used in all calculations. The final R1 was 0.0448 ($I > 2\sigma(I)$) and wR2 was 0.1236 (all data).

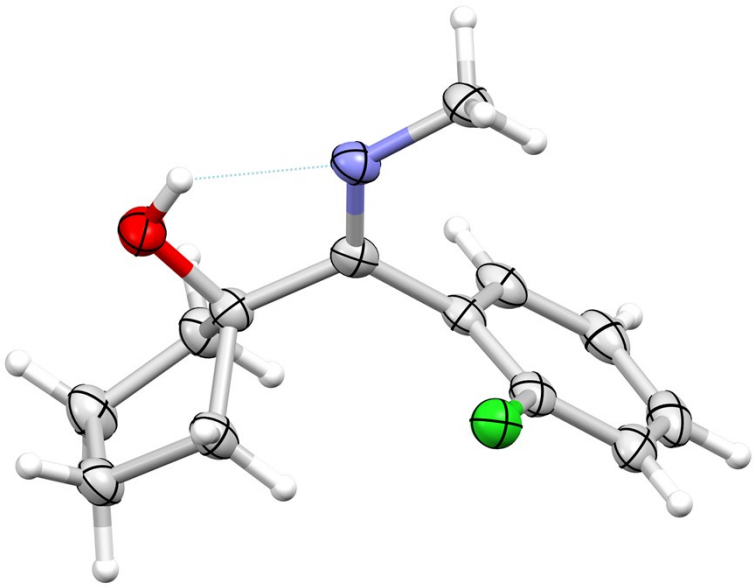


Figure S49. Asymmetric unit of the crystal structure of **4a**, showing thermal displacement ellipsoids at the 50% probability level. An intramolecular hydrogen bond is formed between the OH and N.

2.8.2.3 Crystal data for compound **1a**.

$C_{13}H_{16}ClNO$, M = 237.72, monoclinic, space group $P2_1/c$ (No. 14), a = 10.0679(3) Å, b = 8.2104(3) Å, c = 28.6875(9) Å, β = 98.842(3)°, V = 2343.17(13) Å^3, Z = 8, T = 100 K, ρ_{calc} = 1.348 g cm^{-3}, μ(Cu-Kα) = 2.696 mm^{-1}, F(000) = 1008, 21941 reflections measured, 4776 unique (R_{int} = 0.0567) which were used in all calculations. The final R1 was .0423 ($I > 2\sigma(I)$) and wR2 was 0.1261 (all data).

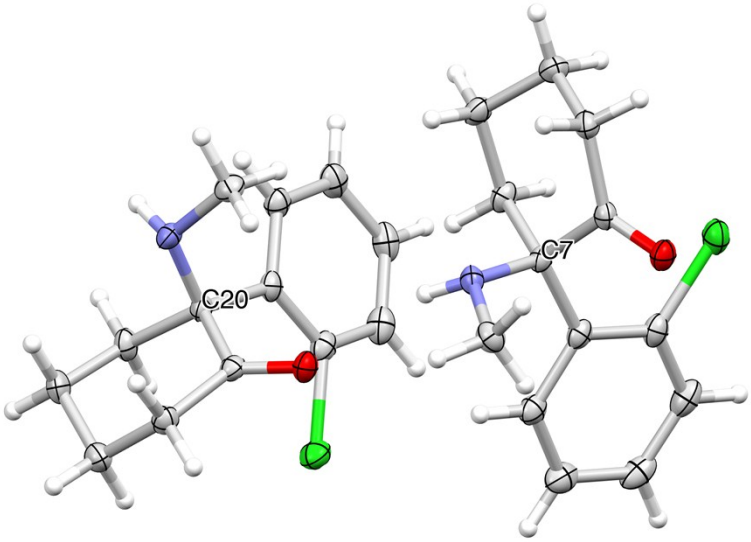


Figure S50. Asymmetric unit of the crystal structure of **1a**, showing thermal displacement ellipsoids at the 50% probability level. The asymmetric unit contains two different molecules, i.e. the first molecule has chirality at C7 (*R*) and the second molecule has chirality at C20 (*S*).

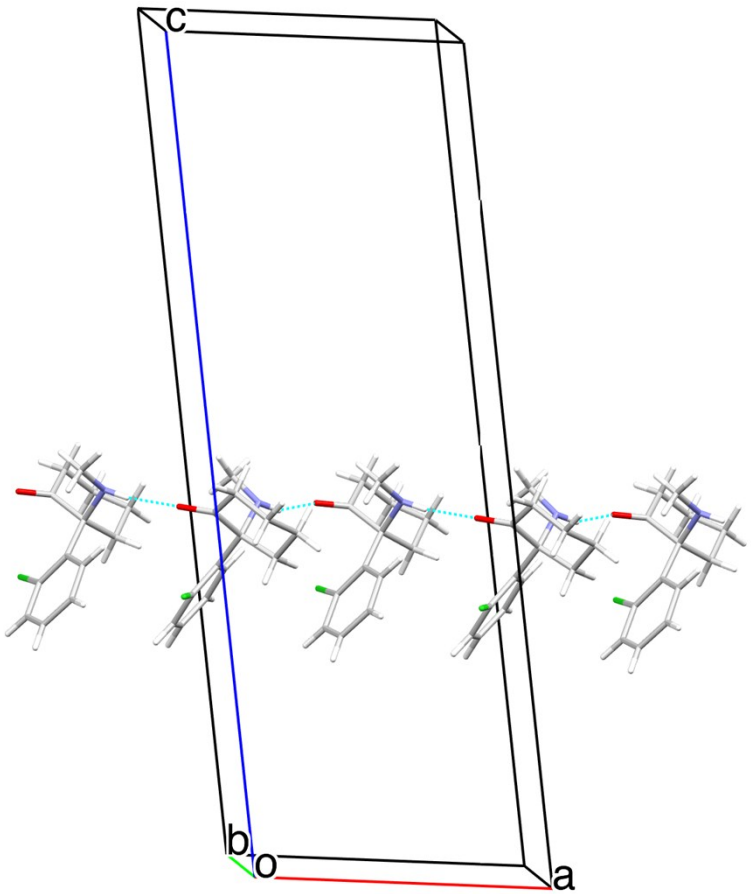
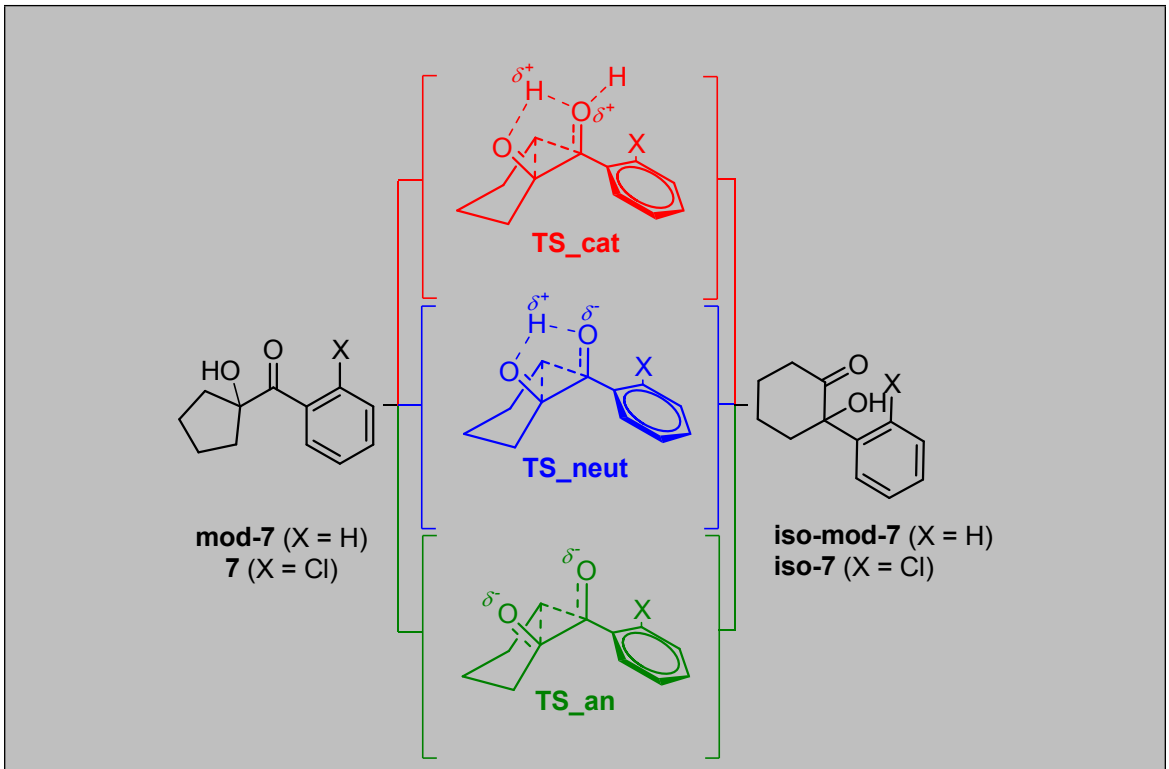


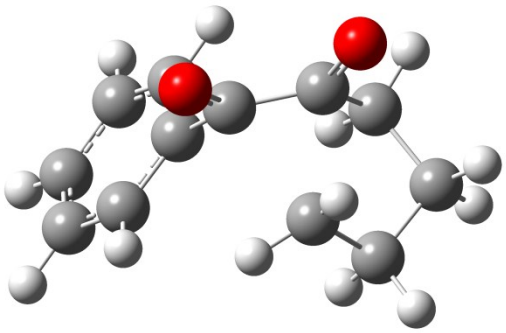
Figure S51. Hydrogen bonds formed, between N-H and C=O functional groups in the crystal structure of **1a**, forming chains along the [100] direction.

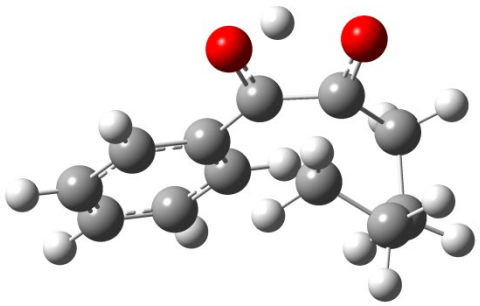
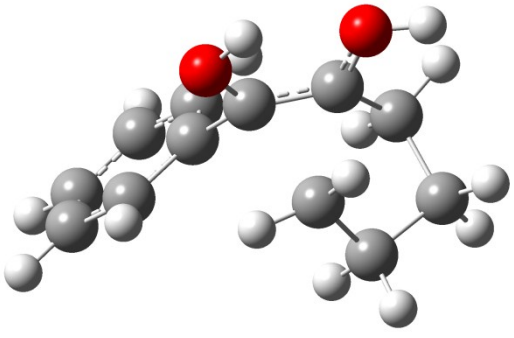
3 Computations

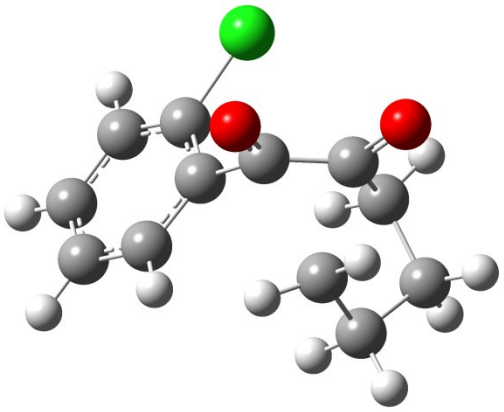
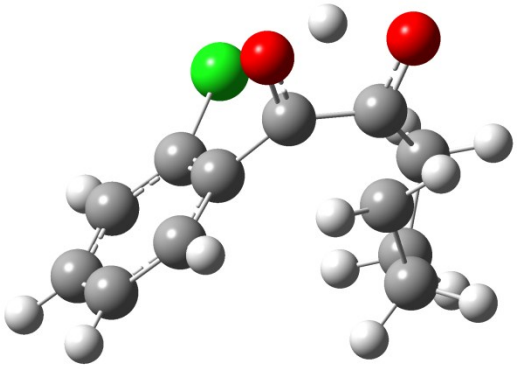
3.1 α-Ketol rearrangement on hydroxy cyclopentylphenylketones mod-7 and 7

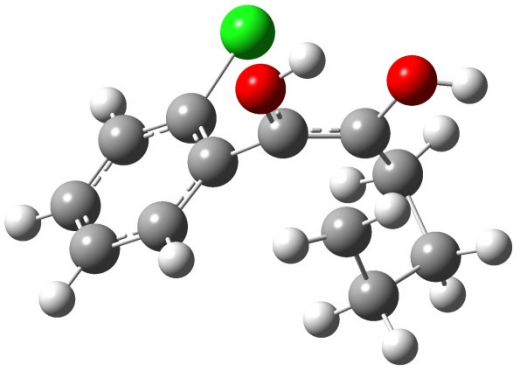
Rearrangements of hydroxy cyclopentylphenylimines **mod-7** and **7** under basic (**TS_an**), neutral (**TS_neut**) and cationic (**TS_cat**) conditions.



TSmod-7_an	**B3LYP/6-31+G**** (Hartree)
27 scf done: -615.672897 C 0.006809 0.010091 -0.017377 C -0.001725 0.036304 1.466442 O 1.067407 0.137051 2.123517 O 1.102663 0.031221 -0.683032 C -0.516282 1.992120 0.548534 C -1.323179 0.012671 2.239963 C -1.657876 1.438366 2.715389 C -1.697528 2.312470 1.454187 C -1.195498 -0.519055 -0.795957 C -1.769435 -1.766388 -0.494848 C -2.777536 -2.314136 -1.298284 C -3.232626 -1.622389 -2.423735 C -2.652448 -0.389681 -2.751617 C -1.639234 0.142490 -1.950943 H 0.456488 2.312921 0.936003 H -0.646944 2.310500 -0.488799 H -2.148462 -0.350635 1.623240 H -1.201706 -0.674187 3.086960 H -0.877727 1.789203 3.402606 H -2.609859 1.466896 3.261461 H -1.712227 3.380702 1.725012 H -2.633359 2.119908 0.912276	H = -615.439776 G = -615.490344 

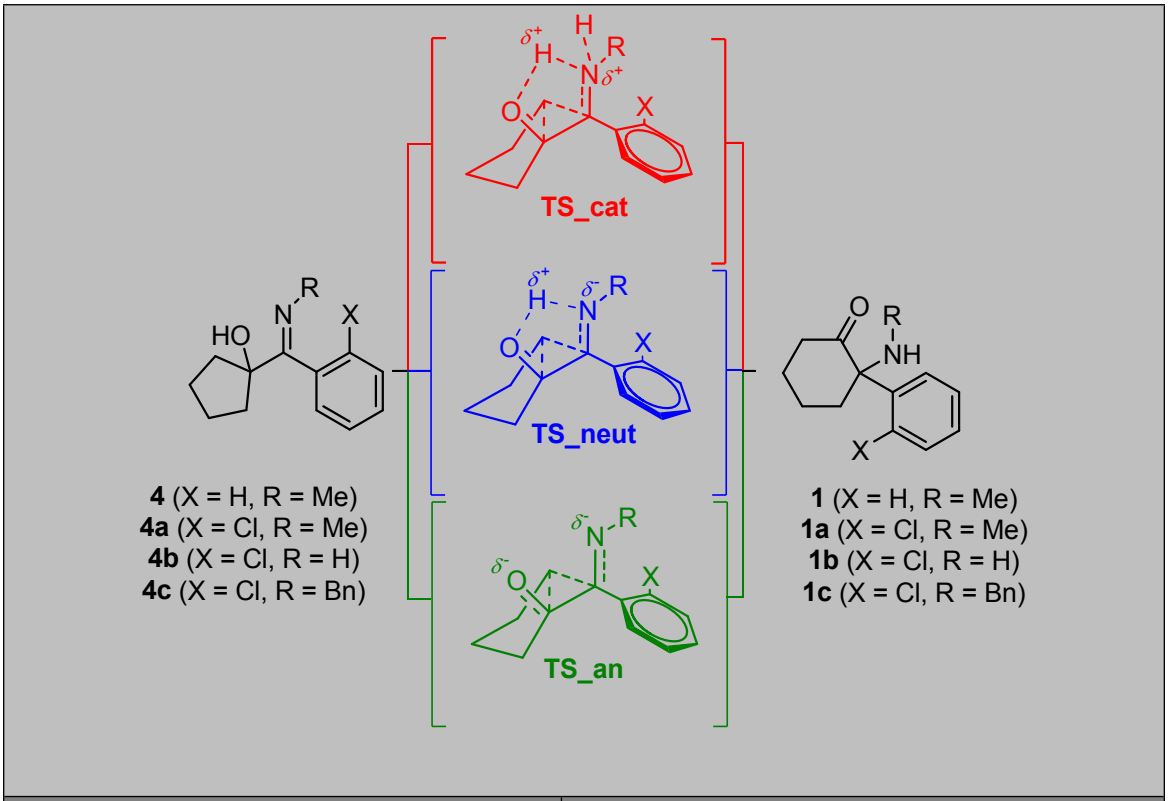
H -1.424807 -2.321821 0.374735 H -3.206935 -3.279345 -1.040671 H -4.020892 -2.039976 -3.045964 H -2.987953 0.153167 -3.629972 H H -1.183883 1.089489 -2.228366 H	
TSmod-7_neut	**B3LYP/6-31+G**** (Hartree)
28 scf done: -616.142449 C -0.013758 0.033127 -0.029110 C -0.024288 0.047423 1.427642 O 1.178806 0.122046 1.926162 O 1.207724 0.272198 -0.476343 C -0.675304 1.856027 1.016255 C -1.159800 -0.437254 2.331451 C -2.298433 0.597293 2.367570 C -1.599918 1.956720 2.221340 C -1.033327 -0.261055 -1.051330 C -2.170956 -1.044161 -0.788248 C -3.083539 -1.325500 -1.806068 C -2.878569 -0.827679 -3.096004 C -1.746741 -0.051824 -3.368995 C -0.828466 0.225439 -2.357967 H 1.709956 0.285420 0.426298 H 0.271436 2.391632 1.068222 H -1.196235 2.054809 0.079991 H -1.497817 -1.439023 2.049012 H -0.707186 -0.524460 3.323134 H -2.878624 0.523613 3.292834 H -2.995506 0.447433 1.535184 H -2.319592 2.773659 2.089455 H -1.015859 2.168392 3.124263 H -2.342855 -1.454528 0.197914 H -3.952388 -1.939220 -1.589654 H -3.592870 -1.046311 -3.883983 H -1.578426 0.335576 -4.369095 H 0.051194 0.821825 -2.572595	H = -615.897159 G = -615.947923 
TSmod-7_cat	**B3LYP/6-31+G**** (Hartree)
29 scf done: -616.585454 C 0.008432 -0.048127 -0.021965 C 0.018446 0.058284 1.389043 O 1.257385 0.101651 1.906793 O 1.176912 0.001687 -0.686740 C -0.405943 1.857555 0.528345 C -1.171627 -0.018479 2.312143 C -1.658046 1.420354 2.613249 C -1.700503 2.124000 1.255260 C -1.114910 -0.555052 -0.857938 C -1.804805 -1.719441 -0.485857 C -2.788478 -2.246043 -1.325226 C -3.086418 -1.619187 -2.537776 C -2.385198 -0.471285 -2.921301 C -1.396534 0.054636 -2.090886 H 1.920252 0.164687 -0.077252 H 1.262789 0.305974 2.855716 H 0.493608 2.275461 0.982454 H -0.416737 2.069406 -0.538758 H -1.978530 -0.573041 1.834909 H -0.880287 -0.564275 3.213964 H -0.962440 1.928068 3.290376 H -2.634413 1.394878 3.102528	H = -616.325748 G = -616.376817 

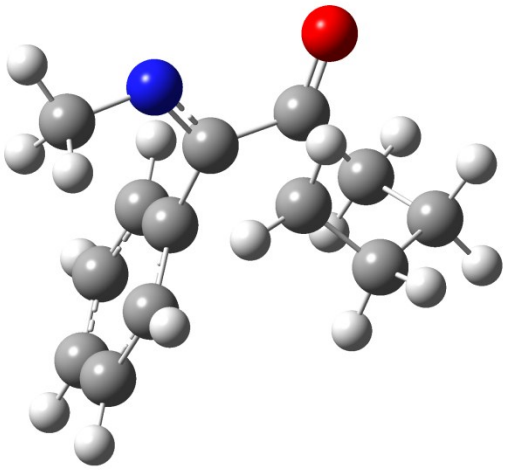
H -1.808427 3.210898 1.364035 H -2.548859 1.774203 0.658059 H -1.560896 -2.233709 0.437443 H -3.314038 -3.149119 -1.032158 H -3.854826 -2.028118 -3.186390 H -2.603490 0.012143 -3.868024 H -0.844705 0.933639 -2.407856	
TS7_an	**B3LYP/6-31+G**** (Hartree)
27 scf done: -1075.264874 C 0.003858 -0.004053 -0.006535 C -0.000181 0.015059 1.469532 O 1.091712 0.016911 2.130681 O 1.048449 0.143491 -0.698995 C -0.544293 1.946529 0.899411 C -1.303393 -0.219930 2.247570 C -1.728038 1.106081 2.904343 C -1.777484 2.134513 1.764626 C -1.233440 -0.458722 -0.778970 C -1.594611 -1.814424 -0.820531 C -2.643375 -2.291579 -1.608947 C -3.362451 -1.397190 -2.403542 C -3.013924 -0.043841 -2.407680 C -1.959628 0.407754 -1.612180 Cl -0.694756 -3.003094 0.140159 H -0.636968 2.327431 -0.118578 H 0.387334 2.300055 1.343852 H -2.111712 -0.559099 1.591238 H -1.119222 -1.003894 2.989372 H -0.978032 1.402118 3.649017 H -2.688904 1.016433 3.425747 H -1.847945 3.160110 2.158998 H -2.681104 1.966705 1.163395 H -2.886504 -3.348721 -1.602515 H -4.180721 -1.760854 -3.017475 H -3.558984 0.659573 -3.030087 H -1.692041 1.458343 -1.635578	H = -1075.041237 G = -1075.094899 
TS7_neut	**B3LYP/6-31+G**** (Hartree)
28 scf done: -1075.727877 C 0.002304 -0.008287 -0.011020 C 0.008145 0.068746 1.440722 O 1.237185 0.066643 1.898133 O 1.221881 0.106933 -0.477682 C -0.603585 1.815438 1.011466 C -1.152111 -0.329626 2.340860 C -2.441372 0.373025 1.901404 C -2.051295 1.816934 1.496766 C -1.072588 -0.329953 -0.987420 C -1.533160 -1.652647 -1.113111 C -2.503302 -2.001681 -2.051879 C -3.022731 -1.021528 -2.898894 C -2.557053 0.292752 -2.816711 C -1.584857 0.629291 -1.875838 Cl -0.851123 -2.929785 -0.109773 H 1.718693 0.113622 0.466614 H 0.125027 2.246552 1.697131 H -0.437777 2.247271 0.025458 H -0.864604 -0.016602 3.350180 H -1.253679 -1.419237 2.354071 H -3.188726 0.363483 2.700378	H = -1075.4919590 G = -1075.5465110 

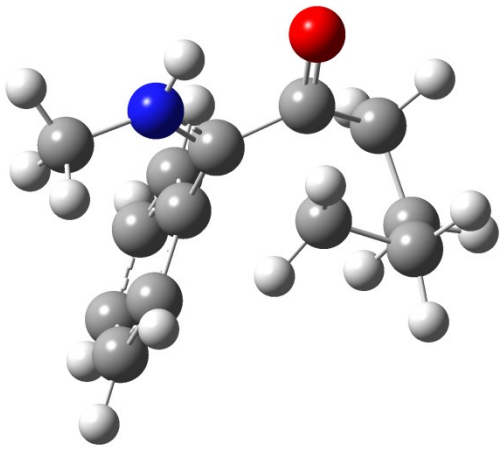
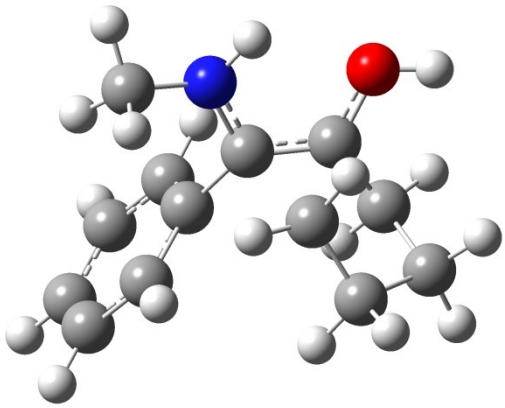
H -2.886400 -0.145041 1.046810 H -2.731640 2.206439 0.733866 H -2.128258 2.478923 2.366658 H -2.838762 -3.030380 -2.120521 H -3.780650 -1.291864 -3.627098 H -2.944822 1.055111 -3.484148 H -1.222259 1.649719 -1.826920	
TS_7_cat	**B3LYP/6-31+G**** (Hartree)
29 scf done: -1076.173130 C 0.031988 -0.077691 -0.019784 C 0.020448 0.085856 1.382961 O 1.253243 0.117683 1.923852 O 1.193464 -0.068816 -0.680901 C -0.371751 1.847799 0.547952 C -1.196386 -0.018253 2.271284 C -1.701965 1.410198 2.578117 C -1.687980 2.137095 1.230263 C -1.110694 -0.602266 -0.826646 C -1.505765 -1.944453 -0.668979 C -2.515754 -2.496915 -1.454774 C -3.136239 -1.712769 -2.428217 C -2.736260 -0.389394 -2.624117 C -1.725933 0.155602 -1.833883 Cl -0.698870 -2.983203 0.498386 H 1.943336 0.068306 -0.070726 H 1.244014 0.343981 2.867497 H 0.516771 2.263211 1.024751 H -0.331941 2.059458 -0.518750 H -1.977946 -0.577694 1.754028 H -0.927150 -0.578857 3.170428 H -1.035903 1.907259 3.291865 H -2.697849 1.376765 3.025577 H -1.775748 3.224317 1.349320 H -2.522874 1.812234 0.601438 H -2.801957 -3.532276 -1.309575 H -3.923647 -2.143918 -3.037694 H -3.204484 0.218677 -3.390351 H -1.418195 1.180449 -2.005747	H = -1075.921905 G = -1075.975962 

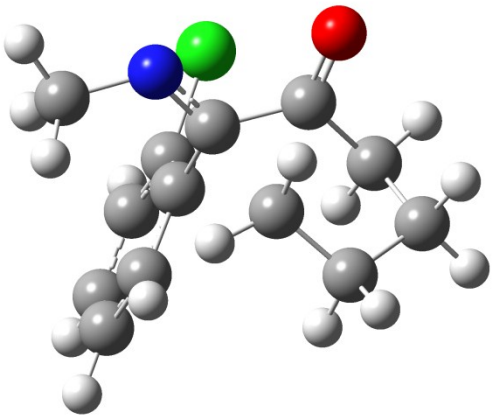
3.2 α-Iminol rearrangement on α-hydroxy cyclopentylphenylimines 4¸4a, 4b and 4c

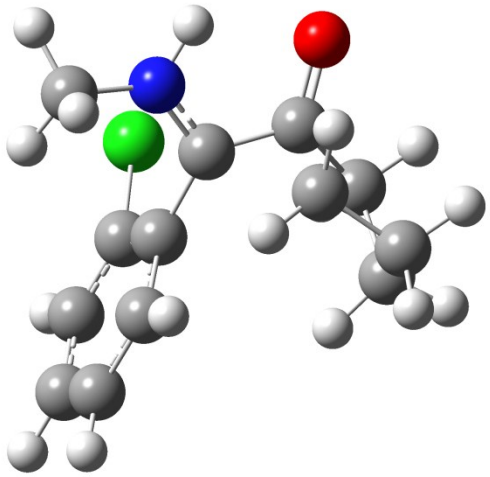
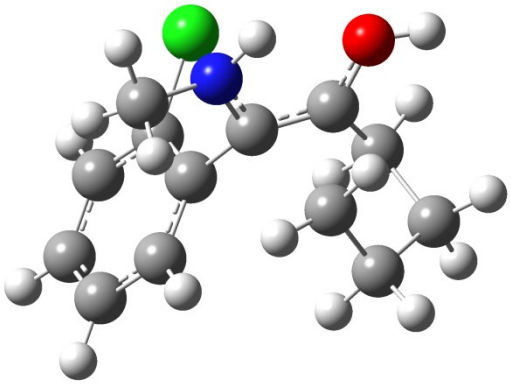
Rearrangements of α-hydroxy cyclopentylphenylimines **4**, **4a**, **4b** and **4c** under basic (**TS_an**), neutral (**TS_neut**) and cationic (**TS_cat**) conditions.

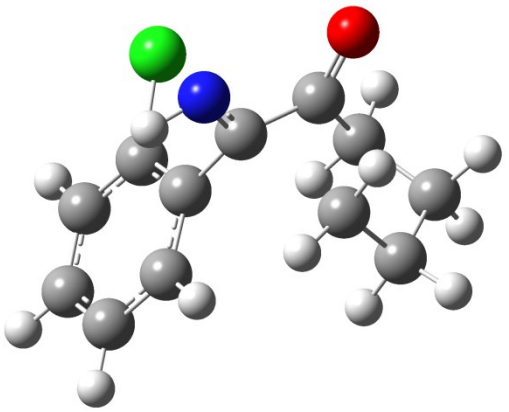
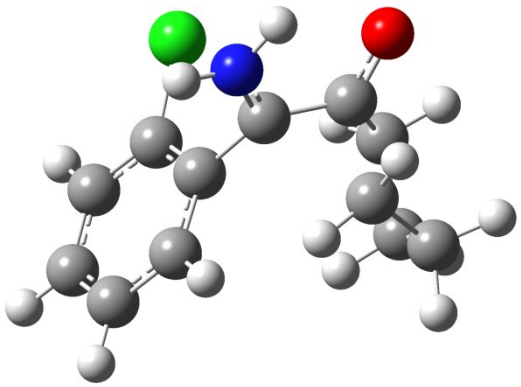


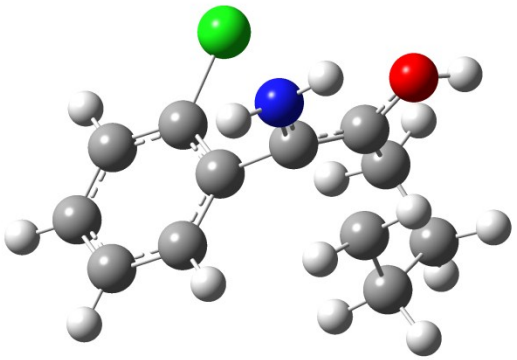
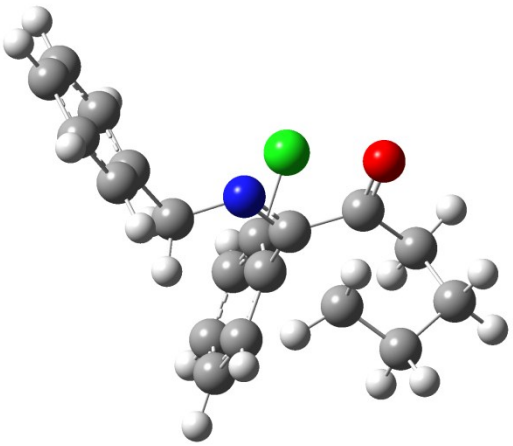
TS4_an	**B3LYP/6-31+G**** (Hartree)
31 scf done: -635.074257 C 0.133297 -0.055754 -0.012771 C 0.022358 0.213896 1.443917 O 1.014053 0.529235 2.149442 N 1.341642 -0.010142 -0.585863 C 1.419233 -0.222558 -2.023632 C -0.718456 1.885782 0.130697 C -1.338556 0.116040 2.140122 C -1.945072 1.528340 2.274481 C -2.027264 2.126634 0.862857 C -0.948530 -0.928694 -0.632720 C -0.955984 -2.290658 -0.275166 C -1.856102 -3.191403 -0.849453 C -2.771674 -2.750524 -1.812391 C -2.766134 -1.405713 -2.191580 C -1.861788 -0.508274 -1.610294 H 0.131747 2.441757 0.532923 H -0.771820 2.021537 -0.951668 H -2.036234 -0.515596 1.583069 H -1.179008 -0.338371 3.124261 H -1.289457 2.142055 2.906414 H -2.926961 1.495164 2.763873 H -2.278690 3.199403 0.920825 H -2.850103 1.647457 0.315058 H 0.940778 0.581456 -2.615425 H 0.974058 -1.170376 -2.379689 H 2.475192 -0.237768 -2.322858 H -0.246251 -2.644323 0.469059	H = -634.801574 G = -634.855478 

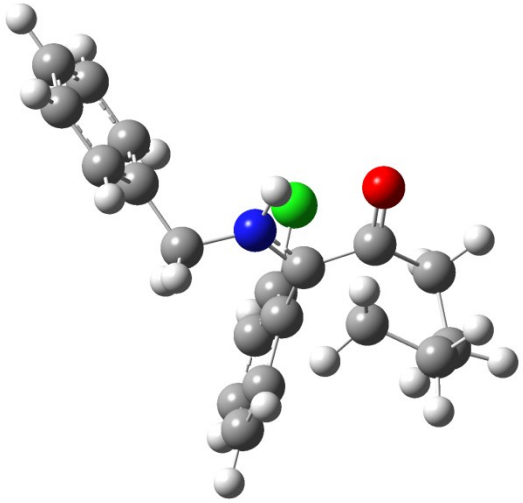
H -1.843393 -4.234955 -0.545753 H -3.475057 -3.446012 -2.261715 H -3.466214 -1.049488 -2.942969 H -1.875892 0.529125 -1.925081	
TS4_neut	**B3LYP/6-31+G**** (Hartree)
32 scf done: -635.586253 C -0.000412 -0.001650 -0.002157 C 0.002037 -0.001103 1.461068 O 1.140928 0.007359 2.056833 N 1.212081 0.139468 -0.554146 C -0.597098 1.865723 1.011503 C -1.244373 -0.436771 2.249830 C -2.395683 0.566593 2.086976 C -1.726360 1.950326 2.029521 C 1.541579 0.395414 -1.949537 C -1.148800 -0.423460 -0.865279 C -1.555078 -1.767270 -0.800381 C -2.580860 -2.241140 -1.621677 C -3.213989 -1.379386 -2.521967 C -2.805331 -0.045342 -2.605327 C -1.775580 0.427754 -1.788097 H 0.352699 2.325479 1.280406 H -0.905233 2.183922 0.016501 H -1.545848 -1.453641 1.977055 H -0.919226 -0.465030 3.294303 H -3.116954 0.488174 2.908479 H -2.943738 0.382064 1.156212 H -2.448081 2.734864 1.770414 H -1.318610 2.192732 3.018432 H 1.938235 0.243992 0.154998 H 2.580266 0.103537 -2.114185 H 1.430953 1.455081 -2.208630 H 0.904591 -0.196008 -2.609621 H -1.061398 -2.447121 -0.113018 H -2.882523 -3.282227 -1.556630 H -4.015098 -1.745598 -3.156956 H -3.284067 0.629724 -3.308268 H -1.467434 1.464205 -1.875146	H = -635.297949 G = -635.353564 
TS4_cat	**B3LYP/6-31+G**** (Hartree)
33 scf done: -636.034649 C -0.004011 -0.084374 0.014307 C 0.007683 -0.312712 1.423696 O 1.215899 -0.426371 1.966629 N 1.206778 -0.110045 -0.644484 C 1.369897 0.367877 -2.017906 C -0.311755 1.666647 0.790279 C -1.211105 -0.433759 2.289154 C -1.577558 0.978430 2.819094 C -1.568879 1.904845 1.601902 C -1.467563 -1.882190 -0.870282 C -2.522200 -2.364767 -1.645778 C -3.332411 -1.474642 -2.357854 C -3.077111 -0.103447 -2.293388 C -2.019840 0.382490 -1.517856 C -1.212981 -0.502280 -0.793647 H 1.188506 -0.450813 2.937642 H 2.018345 0.015346 -0.051912 H 0.666393 -0.138023 -2.681118 H 1.229060 1.452394 -2.111259	H = -635.732102 G = -635.786391 

H 2.383349 0.121413 -2.337882 H 0.619142 1.935857 1.291733 H -0.318739 2.115312 -0.203485 H -1.007042 -1.137930 3.101098 H -2.040236 -0.829683 1.700424 H -2.550182 0.951180 3.316471 H -0.838497 1.306977 3.558659 H -1.583110 2.959101 1.907425 H -2.457962 1.738353 0.986231 H -0.835840 -2.579173 -0.326872 H -2.708318 -3.433165 -1.692947 H -4.154567 -1.848290 -2.960354 H -3.696714 0.594782 -2.847197 H -1.840698 1.451222 -1.492479	
TS4a_an	**B3LYP/6-31+G**** (Hartree)
31 scf done: -1094.667853 C -0.000871 0.001892 -0.000112 C 0.002428 -0.002594 1.487159 O 1.063436 0.004703 2.157749 N 1.162327 -0.035772 -0.655990 C 1.133924 -0.003995 -2.110239 C -0.480455 1.997299 0.555792 C -1.324173 0.002450 2.251719 C -1.663853 1.445742 2.679640 C -1.695836 2.308960 1.411089 C -1.251805 -0.535349 -0.686384 C -1.559718 -1.908222 -0.645110 C -2.642978 -2.466497 -1.326658 C -3.461498 -1.646487 -2.105213 C -3.177516 -0.282114 -2.191127 C -2.090768 0.251352 -1.495029 Cl -0.567746 -3.024659 0.314366 H 0.470852 2.301659 0.998611 H -0.539581 2.359265 -0.472861 H -2.146185 -0.387315 1.643567 H -1.208530 -0.649064 3.124337 H -0.884120 1.809737 3.361604 H -2.614900 1.484207 3.225900 H -1.748730 3.377163 1.682064 H -2.612771 2.090640 0.846659 H 0.745480 0.944916 -2.527319 H 0.541883 -0.810280 -2.583072 H 2.159870 -0.108056 -2.485488 H -2.838928 -3.530454 -1.246808 H -4.304659 -2.075122 -2.638381 H -3.798794 0.369391 -2.798785 H -1.885850 1.311416 -1.578680	H = -1094.403469 G = -1094.460172 
TS4a_neut	**B3LYP/6-31+G**** (Hartree)
32 scf done: -1095.176635 C -0.000135 0.003006 -0.005815 C -0.002166 0.017717 1.458144 O 1.135220 0.032743 2.055215 N 1.201679 0.158964 -0.567865 C 1.507921 0.427330 -1.966550 C -0.596129 1.873607 1.023317 C -1.251292 -0.435659 2.233141 C -2.399778 0.576662 2.096465 C -1.727801 1.959362 2.039027 C -1.140989 -0.462155 -0.859886	H = -1094.896776 G = -1094.955431

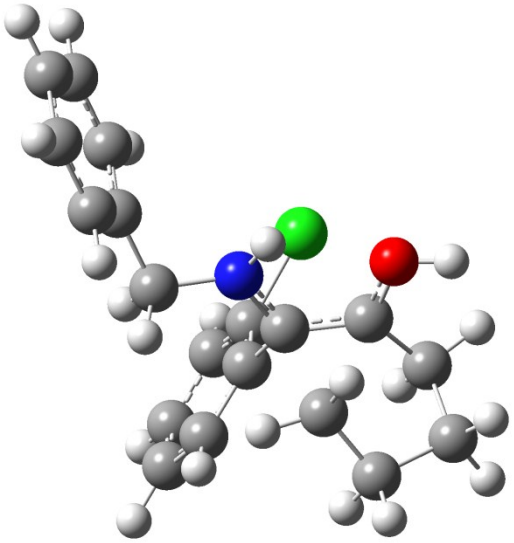
C -1.352840 -1.845995 -1.015991 C -2.380384 -2.351357 -1.812680 C -3.220594 -1.468740 -2.492677 C -3.017777 -0.092364 -2.380046 C -1.987371 0.398350 -1.577359 Cl -0.292385 -3.006480 -0.215934 H 0.357721 2.318881 1.300770 H -0.887966 2.211663 0.030239 H -1.552720 -1.442892 1.926279 H -0.928475 -0.497558 3.276780 H -3.108561 0.495700 2.928390 H -2.964443 0.401215 1.174242 H -2.447626 2.745315 1.779636 H -1.318895 2.200815 3.027556 H 1.935544 0.269405 0.132867 H 2.516935 0.067359 -2.175595 H 0.807902 -0.097714 -2.618260 H 1.463158 1.499576 -2.190503 H -2.513766 -3.423908 -1.899412 H -4.021810 -1.860187 -3.111366 H -3.656269 0.602512 -2.915739 H -1.841207 1.469411 -1.510683	
TS4a_cat	**B3LYP/6-31+G**** (Hartree)
33 scf done: -1095.624808 C 0.002439 -0.003499 -0.001915 C -0.002903 0.003889 1.425552 O 1.199502 0.008747 1.991441 N 1.215219 -0.109628 -0.640227 C 1.391547 0.116737 -2.074471 C -0.350796 1.851636 0.486892 C -1.233057 -0.005517 2.283905 C -1.646085 1.462092 2.573589 C -1.630174 2.185049 1.225059 C -1.191187 -0.559565 -0.744105 C -1.486345 -1.932255 -0.630464 C -2.535532 -2.516160 -1.339097 C -3.310178 -1.729812 -2.193030 C -3.027318 -0.371148 -2.337353 C -1.975644 0.201763 -1.621414 Cl -0.525747 -2.970487 0.418114 H 1.159884 0.141913 2.953268 H 2.023935 0.098136 -0.067862 H 1.231167 1.163321 -2.362877 H 0.711672 -0.516658 -2.646690 H 2.415232 -0.159788 -2.330317 H 0.563059 2.211674 0.961882 H -0.336525 2.142116 -0.563345 H -2.044337 -0.513581 1.759598 H -1.023748 -0.563947 3.200552 H -0.934454 1.924262 3.266859 H -2.629656 1.486493 3.048946 H -1.673283 3.273661 1.358957 H -2.501728 1.902337 0.626829 H -2.737307 -3.574936 -1.223036 H -4.127153 -2.184246 -2.744034 H -3.618696 0.245670 -3.005452 H -1.768441 1.256435 -1.757405	H = -1095.331001 G = -1095.388259 
TS4b_an	**B3LYP/6-31+G**** (Hartree)
28 scf done: -1055.367994	H = -1055.132345

C 0.004026 -0.012065 -0.008742 C 0.003609 0.030887 1.470326 O 1.070648 0.046575 2.138581 N 1.156933 -0.049275 -0.690742 C -0.465868 2.001660 0.543806 C -1.321851 0.042623 2.238189 C -1.654678 1.486295 2.666144 C -1.678805 2.339408 1.390932 C -1.226615 -0.532797 -0.727922 C -1.636197 -1.874712 -0.613005 C -2.692504 -2.409522 -1.352789 C -3.374634 -1.600040 -2.263029 C -2.984223 -0.268451 -2.422242 C -1.928355 0.245031 -1.666987 H 0.489011 2.313888 0.972903 H -0.526977 2.320153 -0.497453 H -2.147134 -0.340649 1.629907 H -1.209507 -0.612851 3.108098 H -0.874191 1.849506 3.347387 H -2.606716 1.531822 3.209754 H -1.719139 3.411064 1.647701 H -2.595508 2.122536 0.825252 H -2.969843 -3.449778 -1.219776 H -4.195715 -2.012407 -2.841416 H -3.499288 0.372398 -3.131823 H -1.634580 1.278661 -1.807484 Cl -0.800126 -2.977656 0.495584 H 0.945813 -0.142906 -1.685107	G = -1055.185582 
TS4b_neut	**B3LYP/6-31+G**** (Hartree)
29 scf done: -1055.868090 C 0.001259 -0.008944 -0.012899 C -0.011300 0.044203 1.448077 O 1.130352 0.062107 2.047998 N 1.191305 0.169951 -0.584415 C -0.599696 1.862457 1.031830 C -1.257957 -0.428210 2.222781 C -2.404946 0.586937 2.099047 C -1.719630 1.962337 2.058679 C -1.121408 -0.454919 -0.898227 C -1.386055 -1.831255 -1.033062 C -2.395763 -2.308207 -1.868601 C -3.158158 -1.404798 -2.610633 C -2.893895 -0.036878 -2.524526 C -1.882974 0.426706 -1.681912 Cl -0.403445 -3.015034 -0.171635 H 0.352955 2.327932 1.278407 H -0.917841 2.169383 0.037173 H -0.930135 -0.497311 3.264342 H -1.558083 -1.432994 1.909372 H -3.116015 0.499196 2.928089 H -2.967700 0.426855 1.172105 H -1.299572 2.186455 3.046493 H -2.426441 2.763044 1.809662 H 1.974553 0.303155 0.050653 H 1.309547 0.274542 -1.581187 H -2.573181 -3.375468 -1.940467 H -3.945679 -1.774767 -3.259344 H -1.684550 1.490923 -1.635910 H -3.469229 0.671695 -3.111275	H = -1055.618000 G = -1055.672771 
TS4b_cat	**B3LYP/6-31+G**** (Hartree)

30 scf done: -1056.318785 C 0.010028 -0.016404 -0.006434 C 0.000466 0.017673 1.414650 O 1.205149 0.031032 1.981948 N 1.213506 -0.109563 -0.656012 C -0.357661 1.859551 0.497326 C -1.231746 -0.004716 2.273242 C -1.656144 1.456210 2.572632 C -1.642680 2.182602 1.225947 C -1.165448 -0.562735 -0.777700 C -1.508731 -1.922234 -0.644096 C -2.537003 -2.491276 -1.393823 C -3.236202 -1.705425 -2.311237 C -2.897670 -0.362438 -2.480536 C -1.869005 0.197597 -1.722322 Cl -0.627382 -2.964057 0.467763 H 1.162460 0.176822 2.941499 H 2.052124 0.187013 -0.173574 H 1.216089 0.029933 -1.656976 H 0.552875 2.225667 0.973875 H -0.337852 2.127461 -0.557094 H -2.039057 -0.514136 1.744072 H -1.019218 -0.570759 3.184344 H -0.949147 1.921598 3.268584 H -2.640719 1.471491 3.046144 H -1.695489 3.270890 1.359368 H -2.507187 1.891590 0.620932 H -2.778978 -3.539797 -1.262759 H -4.036994 -2.149206 -2.893744 H -3.428737 0.252181 -3.199352 H -1.617384 1.240756 -1.874594	H = -1056.054829 G = -1056.108944 
TS4c_an	**B3LYP/6-31+G**** (Hartree)
41 scf done: -1325.737413 C 0.001474 -0.013055 -0.013331 C 0.004138 0.017257 1.472401 O 1.066840 0.019457 2.142468 N 1.167655 -0.068147 -0.660374 C 1.152890 -0.059929 -2.119165 C -0.450926 2.012524 0.540537 C -1.322089 0.039757 2.238383 C -1.646360 1.487744 2.661124 C -1.665459 2.344187 1.387674 C -1.258890 -0.525298 -0.698949 C -1.613505 -1.885636 -0.628160 C -2.708928 -2.422627 -1.307486 C -3.492980 -1.593603 -2.111144 C -3.164367 -0.241109 -2.223233 C -2.066107 0.271608 -1.529952 Cl -0.671520 -3.010226 0.369234 C 2.563516 -0.204938 -2.661350 C 3.352784 0.923543 -2.928887 C 4.662911 0.793837 -3.402688 C 5.207945 -0.476527 -3.618270 C 4.431804 -1.611440 -3.358235 C 3.122488 -1.472338 -2.885513 H 0.503667 2.305100 0.983118 H -0.502463 2.360097 -0.493234 H -2.149234 -0.342616 1.632495 H -1.212938 -0.610763 3.112582 H -0.864015 1.846701 3.342670 H -2.598136 1.539280 3.204909 H -1.707565 3.414697 1.651090	H = -1325.38733800 G = -1325.45714200 

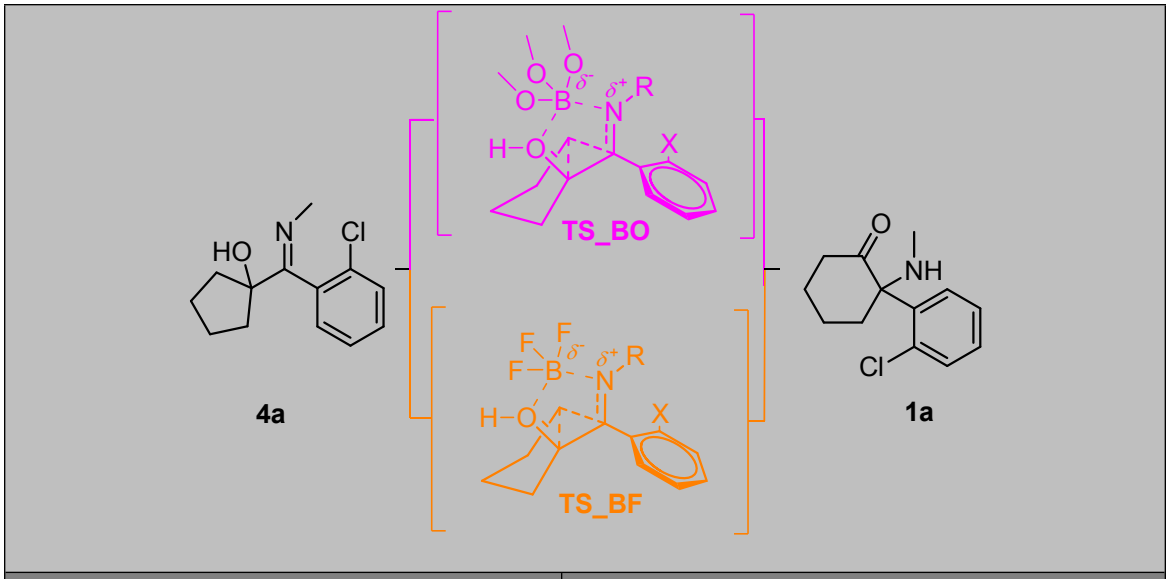
H -2.582221 2.131812 0.820629 H 0.733405 0.879597 -2.524831 H 0.539207 -0.871393 -2.552269 H -2.940818 -3.477397 -1.205431 H -4.345408 -2.005941 -2.642367 H -3.759941 0.417157 -2.848951 H -1.826977 1.322800 -1.633272 H 2.934965 1.914179 -2.764071 H 2.524511 -2.358830 -2.686708 H 5.255773 1.681991 -3.605266 H 4.844230 -2.602959 -3.525903 H 6.224388 -0.580922 -3.987677	
TS4c_neut	**B3LYP/6-31+G**** (Hartree)
42 scf done: -1326.243554 C 0.000000 0.000000 0.000000 C 0.000000 0.000000 1.464590 O 1.136724 0.000000 2.061301 N 1.205065 0.154540 -0.560347 C 1.515523 0.471529 -1.956109 C -0.580179 1.864689 1.048257 C -1.251925 -0.452071 2.236076 C -2.392054 0.571074 2.112741 C -1.707808 1.948060 2.068696 C -1.146322 -0.449743 -0.854913 C -1.369648 -1.830820 -1.020569 C -2.403635 -2.322089 -1.817689 C -3.240891 -1.427857 -2.485980 C -3.028762 -0.053879 -2.361711 C -1.991315 0.422821 -1.559752 Cl -0.316569 -3.005526 -0.231948 C 2.847737 -0.119876 -2.372702 C 3.924658 0.714634 -2.696926 C 5.153551 0.172779 -3.091151 C 5.316215 -1.213016 -3.160957 C 4.245130 -2.054735 -2.836785 C 3.019687 -1.511254 -2.446416 H 0.378333 2.298441 1.327637 H -0.872761 2.216576 0.060214 H -1.561346 -1.453323 1.918053 H -0.927825 -0.528508 3.278294 H -3.099331 0.487524 2.945601 H -2.960459 0.410313 1.190182 H -2.420870 2.743492 1.820037 H -1.293516 2.174614 3.058455 H 1.940649 0.256790 0.141456 H 0.710517 0.076675 -2.581544 H 1.535327 1.559295 -2.095892 H -2.544677 -3.392946 -1.912904 H -4.047547 -1.808368 -3.104397 H -3.665608 0.649944 -2.887556 H -1.837665 1.492290 -1.484273 H 3.803134 1.793515 -2.642518 H 2.191592 -2.168461 -2.194859 H 5.979433 0.832932 -3.339779 H 4.364555 -3.132988 -2.891318 H 6.268859 -1.636216 -3.465955	H = -1325.8779930 G = -1325.9485400 
TS4c_cat	**B3LYP/6-31+G**** (Hartree)
43 scf done: -1326.691723 C 0.002165 0.002653 0.003337	H = -1326.3122880 G = -1326.3825650

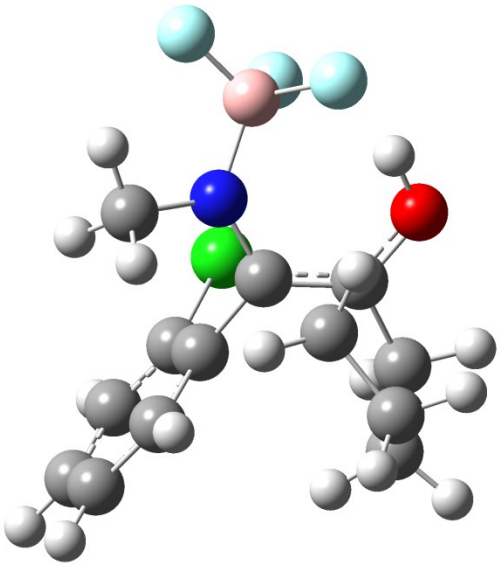
C	-0.006153	-0.010936	1.430304
O	1.194953	-0.011756	1.999699
N	1.218450	-0.089700	-0.632722
C	1.403997	0.181565	-2.068044
C	-0.354908	1.852512	0.532018
C	-1.238222	-0.042665	2.286236
C	-1.653673	1.417438	2.607566
C	-1.635544	2.168958	1.274886
C	-1.190980	-0.538578	-0.750007
C	-1.486494	-1.913148	-0.662659
C	-2.537041	-2.482253	-1.381380
C	-3.312919	-1.678741	-2.217962
C	-3.030434	-0.317326	-2.335232
C	-1.977649	0.240801	-1.609587
C	2.784260	-0.254418	-2.512752
C	3.746771	0.696466	-2.875337
C	5.021209	0.296592	-3.293024
C	5.344606	-1.061412	-3.348083
C	4.388886	-2.018465	-2.985905
C	3.117285	-1.616863	-2.572123
Cl	-0.525421	-2.971478	0.364638
H	1.152377	0.106375	2.963331
H	2.026633	0.115964	-0.056102
H	1.268326	1.248318	-2.289439
H	0.638187	-0.370025	-2.619376
H	0.558778	2.203528	1.013697
H	-0.341539	2.161664	-0.512720
H	-2.047610	-0.540680	1.749523
H	-1.029196	-0.621191	3.190375
H	-0.943956	1.865023	3.312241
H	-2.638337	1.430797	3.081036
H	-1.679474	3.254562	1.431237
H	-2.505600	1.898459	0.668892
H	-2.739031	-3.543048	-1.286086
H	-4.130753	-2.121885	-2.776816
H	-3.622909	0.312990	-2.989584
H	-1.770673	1.298117	-1.724115
H	3.498966	1.754097	-2.835156
H	2.377062	-2.363041	-2.296017
H	5.756647	1.044970	-3.573365
H	4.633175	-3.075801	-3.030858
H	6.332651	-1.374149	-3.672895

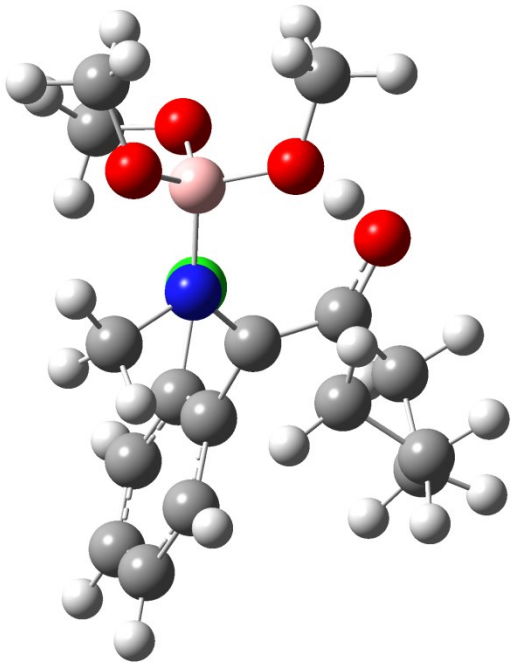


3.3 α-Iminol rearrangement on α-hydroxy cyclopentylphenylimine 4a in the presence of a Lewis acid

Rearrangements of α-hydroxy cyclopentylphenylimine **4a** in the presence of BF_3 (TS_BF) and $B(OMe)_3$ (TS_BO).

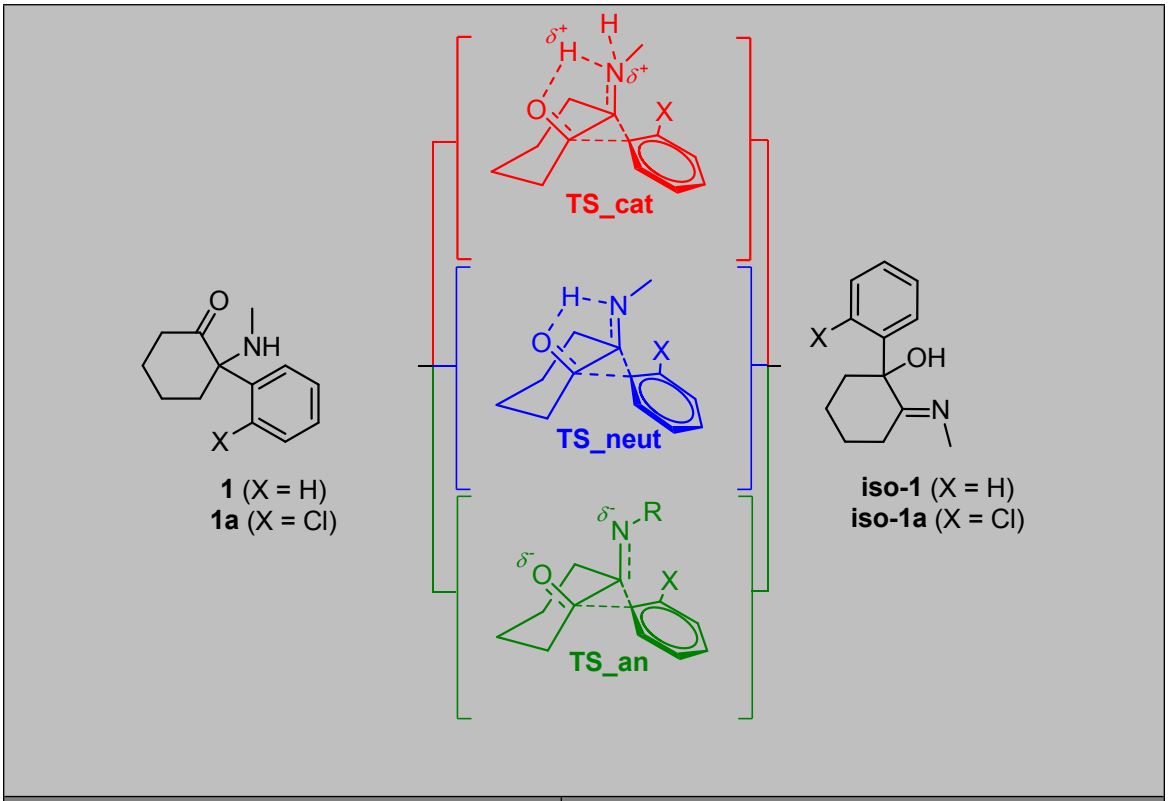


TS4a_BF	**B3LYP/6-31+G**** (Hartree)
36 scf done: -1419.780054 C -0.012049 0.025228 0.008906 C 0.012190 -0.024364 1.449040 O 1.096444 0.022050 2.191335 N 1.123110 -0.043185 -0.788755 C -0.260917 1.847474 0.561658 C -1.247029 -0.117881 2.277841 C -2.194475 1.068656 1.984800 C -1.319031 2.267258 1.586867 C 0.944391 0.355976 -2.195895 B 2.507056 -0.549087 -0.348606 F 3.089799 0.369582 0.643127 F 2.435999 -1.792921 0.307856 F 3.390674 -0.614007 -1.426025 C -1.302688 -0.469519 -0.649588 C -1.606866 -1.845136 -0.633502 C -2.728249 -2.363620 -1.283524 C -3.577426 -1.510015 -1.986462 C -3.296108 -0.144540 -2.032345 C -2.174799 0.358673 -1.372854 Cl -0.578544 -2.989990 0.221539 H -4.448040 -1.913996 -2.493043 H 1.923778 0.422611 -2.663101 H 0.467458 1.338420 -2.279748 H 0.342436 -0.366026 -2.759462 H 0.758871 2.156449 0.783041 H -0.502383 2.151489 -0.454948 H -0.920885 -0.101511 3.319898 H -1.743245 -1.075584 2.099783 H -2.798262 1.293963 2.868248 H -2.884249 0.815157 1.177801 H -0.810368 2.651037 2.477410 H -3.943725 0.533625 -2.578108 H 1.945426 0.122322 1.680810	H = -1419.48117 G =-1419.54698 

H -1.933055 3.078662 1.182643 H -2.926472 -3.428461 -1.235961 H -1.987908 1.423551 -1.431327	
TS4a_BO	**B3LYP/6-31+G**** (Hartree)
48 scf done: -1465.561722 C -0.000186 0.001558 -0.000462 C 0.003270 0.000440 1.450713 O 1.072392 0.001776 2.185870 N 1.113164 -0.060479 -0.818431 C 0.837989 0.216738 -2.242567 C -0.244414 1.888586 0.562805 C -1.287699 -0.049565 2.255996 C -2.196336 1.163995 1.963862 C -1.278968 2.339736 1.593810 B 2.627713 -0.418085 -0.438408 O 2.961720 0.415512 0.796450 O 3.449202 -0.019160 -1.561447 O 2.793622 -1.799583 -0.020515 C 4.253659 0.298457 1.406724 C 4.772052 -0.495532 -1.729295 C 2.573102 -2.811713 -0.984689 C -1.312663 -0.483860 -0.622506 C -1.665995 -1.844108 -0.530786 C -2.816502 -2.359032 -1.132205 C -3.653646 -1.514191 -1.859317 C -3.330778 -0.161528 -1.974576 C -2.179129 0.334783 -1.364507 Cl -0.671768 -2.982387 0.378637 H 4.522609 -0.750699 1.561027 H 0.786459 2.171178 0.766056 H -0.496905 2.172165 -0.457038 H -1.815207 -0.990934 2.083668 H -0.969821 -0.039817 3.301253 H -2.812656 1.396776 2.837925 H -2.877448 0.942469 1.139142 H -1.863171 3.183434 1.208988 H -0.758945 2.684933 2.494416 H 2.009812 0.164261 1.589856 H 1.786183 0.231564 -2.770933 H 0.358416 1.193483 -2.384096 H 0.194611 -0.545026 -2.697740 H -3.048123 -3.412876 -1.025194 H -4.547604 -1.913642 -2.327620 H -3.970282 0.511057 -2.536993 H -1.955876 1.388116 -1.477837 H 2.568877 -3.781128 -0.474806 H 1.607140 -2.688454 -1.491329 H 3.362132 -2.830197 -1.750068 H 4.900960 -0.864744 -2.755425 H 5.494827 0.316686 -1.570498 H 5.012818 -1.310172 -1.036831 H 5.004134 0.781840 0.776085 H 4.218472 0.813941 2.370253	H = -1465.1401340 G =-1465.2182220 

3.4 α-Aminoketone rearrangement on α-amino cyclopentylphenylketones 1 and 1a

Rearrangements of α-amino cyclopentylphenylketones **1** and **1a** under basic (**TS_an**), neutral (**TS_neut**) and cationic (**TS_cat**) conditions.



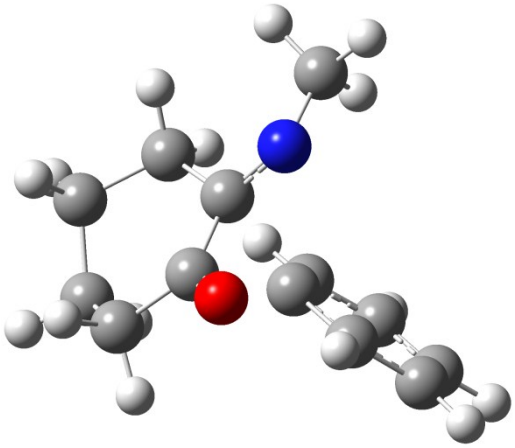
TS1_an	**B3LYP/6-31+G**** (Hartree)

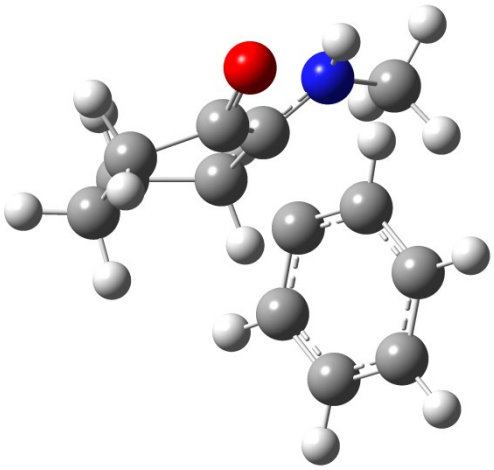
31
scf done:-635.0722014

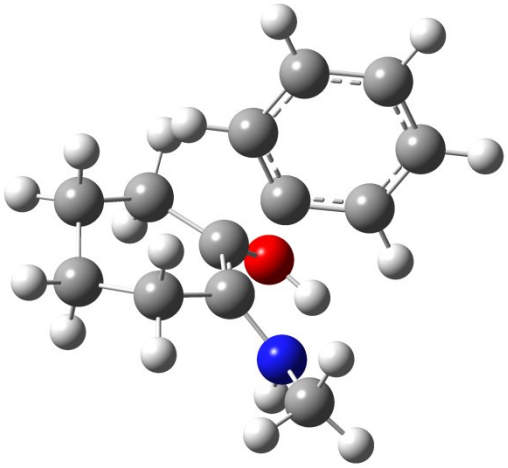
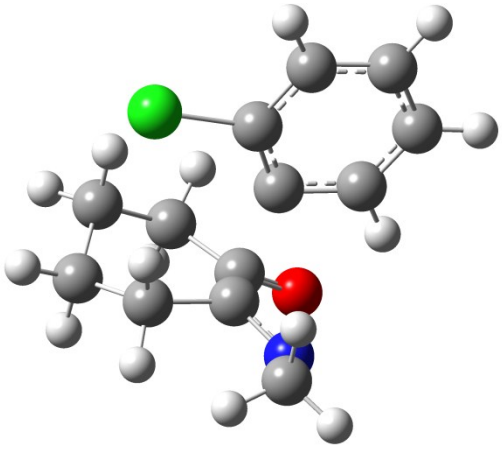
C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.496219
N	1.196728	0.000000	2.108019
O	1.046843	0.144008	-0.658237
C	-0.588037	1.914916	1.200578
C	1.182897	0.059210	3.556070
C	-1.213220	-0.655318	2.191948
C	-2.319749	-1.203763	1.273272
C	-2.580480	-0.299141	0.067946
C	-1.304763	-0.212814	-0.772579
C	-1.548848	2.486859	2.042706
C	-1.596940	3.877012	2.252362
C	-0.699128	4.718823	1.590915
C	0.244537	4.158445	0.715629
C	0.296988	2.772493	0.537519
H	-0.821125	-1.490067	2.784938
H	-1.632707	0.041543	2.925502
H	-1.371411	0.569184	-1.538339
H	-1.166944	-1.158153	-1.319456
H	-3.400425	-0.698093	-0.542575
H	-2.883846	0.699389	0.400792
H	-3.236242	-1.361269	1.856021
H	-2.019417	-2.193325	0.898749
H	2.215891	0.069296	3.927494
H	0.681789	-0.790169	4.063404
H	0.696978	0.974669	3.952968
H	1.023177	2.336058	-0.146901

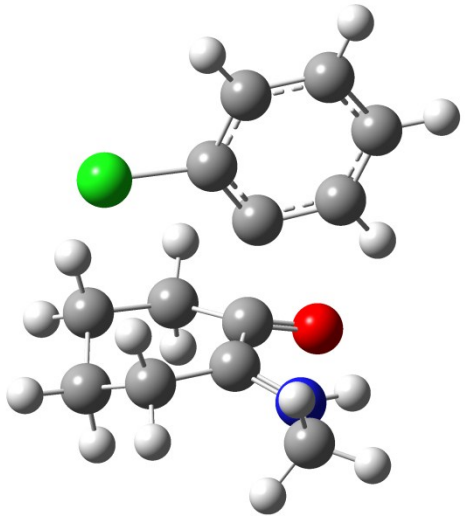
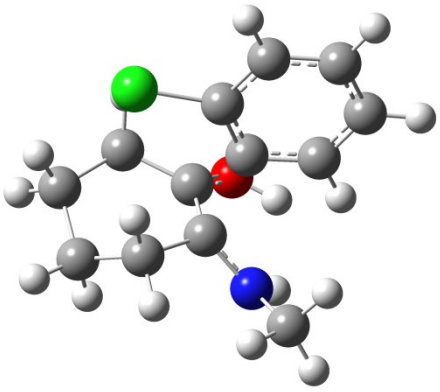
H = -634.798688

G = -634.853079



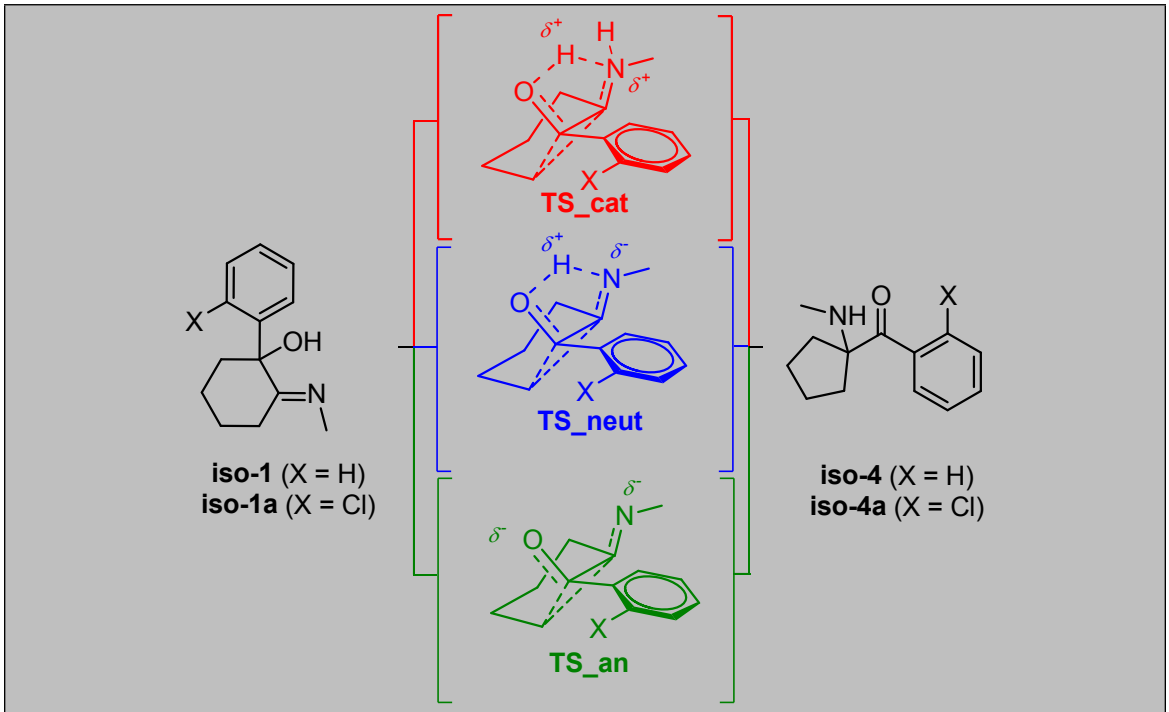
H 0.932343 4.804360 0.172653 H -0.738301 5.794214 1.743962 H -2.341417 4.296001 2.926961 H -2.286922 1.865935 2.550189	
TS1_neut	**B3LYP/6-31+G**** (Hartree)
32 scf done: -635.589253 C 0.004448 0.007503 0.019084 C 0.000569 -0.009453 1.486741 N 1.213075 -0.022735 2.053336 O 1.130994 -0.029256 -0.584877 C -0.389773 1.871992 0.568117 H 0.835328 -0.114424 4.127175 C -1.234024 -0.501844 -0.729274 C -2.505051 -0.719330 0.108697 C -2.171922 -1.289051 1.491791 C -1.232585 -0.364354 2.290450 C -1.604816 2.498443 0.856414 C -1.708963 3.896478 0.800557 C -0.594099 4.673718 0.478123 C 0.626532 4.045693 0.202657 C 0.721398 2.651712 0.243306 C 1.531901 0.347986 3.425449 H -0.910403 -0.870131 3.205032 H -1.764869 0.534593 2.614104 H -1.424952 0.152532 -1.585901 H -0.910595 -1.466227 -1.142937 H -3.167981 -1.408668 -0.426782 H -3.065911 0.214285 0.216156 H -3.086127 -1.451977 2.072918 H -1.691067 -2.269425 1.375830 H 1.955723 0.046293 1.357975 H 2.538004 -0.005623 3.656344 H 1.498063 1.436170 3.563330 H 1.654049 2.156455 -0.014279 H 1.500412 4.639392 -0.053086 H -0.674242 5.756318 0.440833 H -2.662686 4.370774 1.016879 H -2.487475 1.933656 1.135531	H = -635.300190 G = -635.354901 
TS1_cat	**B3LYP/6-31+G**** (Hartree)
33 scf done: -636.025508 C 0.001125 0.000920 0.000347 C -0.001287 0.001852 1.439051 N 1.250575 -0.001594 2.042749 O 1.153939 0.049569 -0.700925 C -0.387034 1.636146 0.743316 C -1.708789 2.096592 0.611556 C -1.964328 3.463447 0.529121 C -0.910709 4.380692 0.590590 C 0.405140 3.926963 0.738463 C 0.667947 2.563351 0.818518 C -1.113641 -0.603855 -0.829073 C -2.308312 -1.170532 -0.034402 C -1.887904 -1.678144 1.347332 C -1.224806 -0.563981 2.177365 C 1.409277 0.337424 3.456793 H -0.867343 -0.965504 3.127715 H -1.949320 0.214879 2.422734 H -1.428636 0.101789 -1.602658 H -0.608658 -1.424424 -1.352128	H = -635.7231240 G =-635.7769560

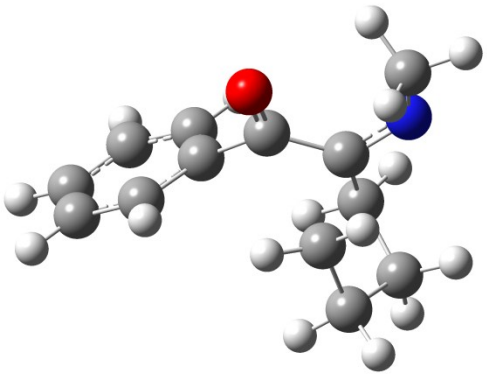
H -2.743492 -1.985487 -0.620634 H -3.101180 -0.423641 0.071891 H -2.758288 -2.055199 1.892962 H -1.188167 -2.516763 1.242471 H 1.867827 -0.738566 1.716080 H 0.964131 -0.401314 4.133932 H 0.954830 1.312743 3.649735 H 2.476543 0.408177 3.672094 H 1.686639 2.226038 0.972175 H 1.224806 4.634574 0.805475 H -1.114440 5.445210 0.533789 H -2.986801 3.808832 0.418286 H -2.542412 1.410061 0.560104 H 1.905880 0.292398 -0.133695	
TS1a_an	**B3LYP/6-31+G**** (Hartree)
31 scf done: -1094.662661 C 0.000000 0.000000 0.000000 C 0.000000 0.000000 1.503280 N 1.198664 0.000000 2.092810 O 1.044517 0.142883 -0.654024 C -0.588044 1.914915 1.200583 C 1.211161 0.067386 3.541882 C -1.192162 -0.712514 2.186707 C -2.198370 -1.397114 1.241947 C -2.546277 -0.545618 0.019809 C -1.278331 -0.281713 -0.792056 C -1.603674 2.690581 1.761565 C -1.557593 4.090282 1.891402 C -0.448466 4.783485 1.417340 C 0.600707 4.058137 0.837472 C 0.518188 2.669353 0.758564 Cl -3.163153 2.001852 2.394212 H -0.757223 -1.488490 2.826974 H -1.712296 -0.029781 2.858537 H -1.413411 0.531966 -1.514302 H -1.034461 -1.173398 -1.387348 H -3.282841 -1.061679 -0.609314 H -3.002283 0.394712 0.336130 H -3.102512 -1.658586 1.805982 H -1.770617 -2.347734 0.889906 H 2.249567 0.058249 3.896286 H 0.696754 -0.764991 4.060105 H 0.751177 0.997788 3.931591 H 1.357514 2.118021 0.340058 H 1.479337 4.573797 0.456651 H -0.404647 5.865476 1.504766 H -2.383752 4.619896 2.356046	H = -1094.397371 G = -1094.455720 
TS1a_neut	**B3LYP/6-31+G**** (Hartree)
32 scf done: -1095.172202 C 0.000000 0.000000 0.000000 C 0.000000 0.000000 1.478299 N 1.210608 0.000000 2.029597 O 1.129432 -0.014470 -0.595380 C -0.403199 1.868500 0.528492	H = -1094.893166 G = -1094.952363

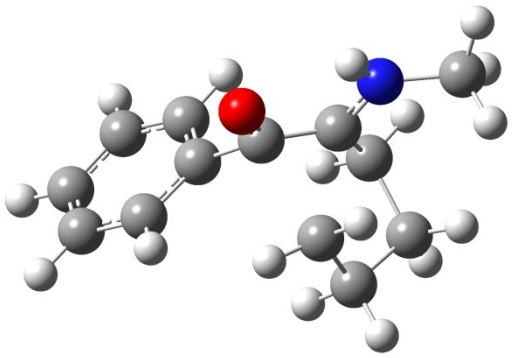
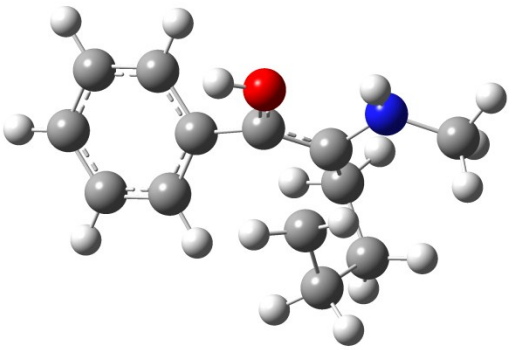
C 1.564816 0.318418 3.406752 C -1.211656 -0.610168 -0.732175 C -2.265857 -1.353446 0.134162 C -1.783612 -1.683764 1.552146 C -1.218274 -0.429811 2.254595 C -1.580796 2.622274 0.548873 C -1.576835 4.025304 0.527306 C -0.367674 4.713957 0.490460 C 0.829942 3.991488 0.463194 C 0.792649 2.599318 0.478568 Cl -3.205463 1.895619 0.573927 H 0.859701 -0.129284 4.108109 H -0.942439 -0.654215 3.286943 H -1.978927 0.350915 2.289414 H -1.694719 0.147418 -1.356041 H -0.742970 -1.318203 -1.422246 H -2.548470 -2.279683 -0.378362 H -3.174745 -0.753131 0.210970 H -2.612192 -2.084818 2.146007 H -1.007095 -2.459708 1.527136 H 1.950111 0.028826 1.326687 H 2.558272 -0.083745 3.610363 H 1.580644 1.403193 3.566355 H 1.724970 2.046156 0.415496 H 1.784322 4.508375 0.422667 H -0.364947 5.799533 0.475688 H -2.519508 4.562587 0.535663	
TS1a_cat	**B3LYP/6-31+G**** (Hartree)
33 scf done: -1095.600453 C -0.001903 0.001421 -0.000082 C 0.002382 -0.002844 1.447658 N 1.215169 -0.003074 2.109517 O 1.069752 0.273576 -0.745605 C 1.371400 0.485965 3.478741 C -0.566734 1.669489 0.954884 C -1.876252 2.185671 0.846104 C -2.104602 3.566129 0.881075 C -1.044708 4.458614 1.007404 C 0.261045 3.971518 1.104235 C 0.482522 2.600998 1.078875 C -1.108424 -0.815491 2.130642 C -1.339041 -2.100710 1.318991 C -1.882307 -1.781022 -0.077039 C -1.063775 -0.689456 -0.819738 Cl -3.317665 1.210470 0.624852 H -0.766909 -1.057565 3.136788 H -2.036894 -0.257884 2.234469 H -1.721125 0.053988 -1.279221 H -0.499892 -1.127622 -1.648305 H -1.880915 -2.684708 -0.693168 H -2.922300 -1.459493 0.008638 H -2.046561 -2.741687 1.853674 H -0.394618 -2.655703 1.250327 H 2.067476 -0.000499 1.567367 H 1.257698 1.575698 3.542983 H 2.368534 0.212371 3.825082 H 0.639276 0.022720 4.142525 H 1.502929 2.254648 1.198282 H 1.100607 4.649355 1.212372 H -1.241228 5.525286 1.030260 H -3.122498 3.929400 0.795953 H 1.811049 0.681288 -0.271357	H = -1095.3066630 G = -1095.3641220 

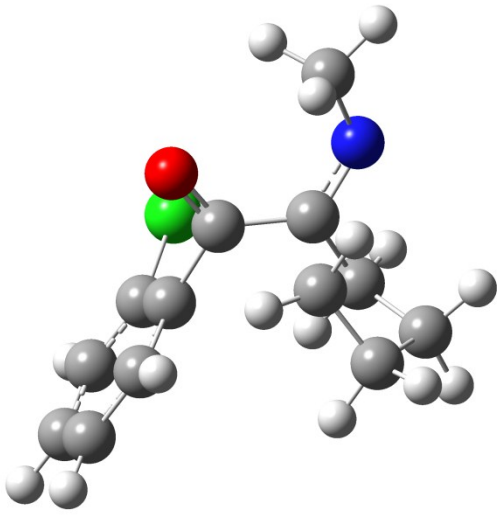
3.5 α-Iminol rearrangement of α-hydroxy cyclopentylphenylimines iso-1 and iso-1a

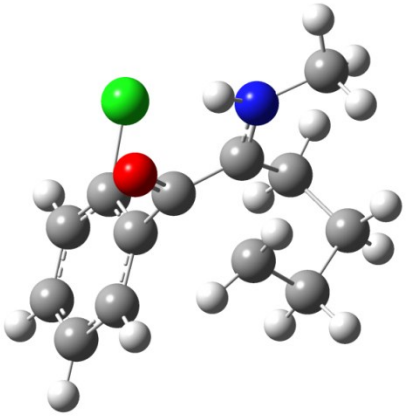
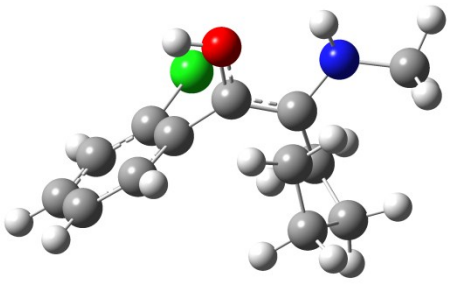
Rearrangements of α-hydroxy cyclopentylphenylimines **iso-1** and **iso-1a** under basic (**TS_an**), neutral (**TS_neut**) and cationic (**TS_cat**) conditions.



TSiso-1_an	**B3LYP/6-31+G**** (Hartree)
31 scf done: -635.067404 C -0.016389 0.019115 -0.005272 C -0.014577 0.004252 1.486023 N 1.089753 -0.009774 2.271967 O 0.956480 0.389484 -0.699355 C 2.338958 0.559526 1.796565 C -0.820139 1.849235 1.271590 C -1.243661 -0.560884 2.220037 C -1.818323 0.540365 3.125083 C -2.023029 1.750601 2.199271 C -1.212732 -0.487534 -0.802309 C -1.559465 -1.847609 -0.763440 C -2.542160 -2.361442 -1.615581 C -3.205158 -1.517877 -2.512532 C -2.864619 -0.161287 -2.562299 C -1.865642 0.343205 -1.725173 H 0.049894 2.351869 1.698965 H -1.047032 2.271868 0.288703 H -0.944942 -1.446113 2.791875 H -2.027454 -0.862282 1.521023 H -2.752959 0.229118 3.609678 H -1.097889 0.778981 3.916385 H -2.933793 1.594269 1.604770 H -2.185083 2.672194 2.780502 H 2.820261 0.023121 0.960436 H 3.058339 0.558370 2.629449 H 2.248386 1.611098 1.460119 H -1.054200 -2.511358 -0.066781 H -2.790086 -3.418701 -1.576328 H -3.975396 -1.913541 -3.168460	H = -634.794932 G = -634.853215 

H -3.371524 0.501981 -3.258109 H -1.589393 1.391735 -1.788424	
TSiso-1_neut	**B3LYP/6-31+G**** (Hartree)
32 scf done: -635.593127 C -0.005178 0.002564 -0.002290 C -0.002788 0.000641 1.457341 N 1.227457 0.004495 2.006969 O 1.107023 0.104387 -0.627922 C -0.572611 1.876776 0.606599 C -1.226475 -0.113623 2.336738 C -1.732169 1.294828 2.724251 C -1.835131 2.087432 1.417114 C 1.575895 0.362109 3.375481 C -1.180021 -0.565152 -0.775198 C -1.680508 -1.839157 -0.463460 C -2.665550 -2.436126 -1.257038 C -3.165420 -1.766341 -2.376924 C -2.660790 -0.503300 -2.706381 C -1.670087 0.085331 -1.917576 H 1.958750 0.068808 1.301400 H 0.327774 2.326692 1.030017 H -0.656583 2.149322 -0.444159 H -2.020403 -0.624831 1.790058 H -0.995058 -0.719295 3.217375 H -1.022974 1.779248 3.406039 H -2.691792 1.227423 3.247194 H -1.984644 3.157768 1.619631 H -2.705762 1.748552 0.842480 H 0.916489 -0.136531 4.089148 H 1.526098 1.444554 3.548619 H 2.596778 0.027326 3.567211 H -1.289717 -2.378142 0.395099 H -3.036981 -3.424193 -1.000461 H -3.933858 -2.225759 -2.991774 H -3.034783 0.021587 -3.580850 H -1.270290 1.054449 -2.199472	H = -635.304541 G = -635.359146 
TSiso-1_cat	**B3LYP/6-31+G**** (Hartree)
33 scf done: -636.029199 C -0.001134 0.001017 0.000147 C 0.000485 0.000702 1.432847 N 1.251223 0.000394 2.033317 O 1.173334 0.320706 -0.535596 C 1.461020 0.299919 3.449085 C -0.681430 1.762370 1.126673 C -1.160323 -0.568294 2.240588 C -1.813676 0.587205 3.023777 C -1.899721 1.769734 2.043385 C -1.039294 -0.510870 -0.924594 C -0.585402 -1.408564 -1.915613 C -1.484323 -1.971425 -2.820536 C -2.839694 -1.638425 -2.764180 C -3.293906 -0.742568 -1.792179 C -2.405196 -0.184362 -0.874437 H 2.000870 0.325594 1.436570 H 0.206515 2.269395 1.503156 H -0.881984 2.105890 0.111759 H -0.788851 -1.362669 2.892626 H -1.887265 -1.021740 1.564102 H -2.798269 0.300392 3.402626 H -1.201625 0.856404 3.889176 H -2.820174 1.714731 1.456707 H -1.925136 2.728512 2.575469	H = -635.726427 G = -635.780951 

H 1.210408 1.335591 3.714595 H 2.517815 0.136248 3.666135 H 0.882802 -0.377900 4.079461 H 0.459179 -1.699749 -1.956561 H -1.121485 -2.671456 -3.565966 H -3.537438 -2.071467 -3.473769 H -4.342810 -0.468246 -1.749080 H -2.782113 0.522166 -0.148967 H 1.108800 0.478597 -1.493302	
TSiso-1a_an	**B3LYP/6-31+G**** (Hartree)
31 scf done: -1094.660992 C 0.003673 -0.009305 -0.001222 C 0.000242 -0.002262 1.488272 N 1.097825 0.004898 2.280461 O 0.973074 0.320081 -0.715569 C 2.332373 0.610551 1.809890 C -0.814314 1.838866 1.257984 C -1.229871 -0.589735 2.202286 C -1.896465 0.514376 3.039125 C -2.085345 1.698889 2.080218 C -1.216964 -0.507408 -0.782686 C -1.414193 -1.877413 -1.004927 C -2.439421 -2.368620 -1.814510 C -3.305142 -1.468787 -2.439421 C -3.124398 -0.095173 -2.256516 C -2.087205 0.371530 -1.446647 H 0.011844 2.323430 1.782152 H -0.952899 2.311342 0.281618 H -0.907009 -1.430379 2.823637 H -1.966759 -0.968465 1.487376 H -2.845518 0.180160 3.477729 H -1.233168 0.796980 3.865713 H -2.935474 1.491626 1.415881 H -2.335285 2.619939 2.630694 H 2.835347 0.082773 0.981560 H 3.045477 0.639153 2.647165 H 2.209498 1.656471 1.465094 H -2.552999 -3.438327 -1.954400 H -4.107384 -1.842799 -3.068097 H -3.786378 0.613273 -2.745659 H -1.948301 1.440174 -1.323893 Cl -0.327160 -3.057882 -0.249486	H = -1094.396961 G = -1094.455191 
TSiso-1a_neut	**B3LYP/6-31+G**** (Hartree)
32 scf done: -1095.184746 C 0.006306 -0.010915 -0.001028 C 0.004234 -0.000851 1.454898 N 1.227238 0.001010 2.018626 O 1.108128 0.069982 -0.639955 C -0.541359 1.872366 0.619925 C -1.236175 -0.130053 2.306583 C -1.758862 1.270888 2.696971 C -1.822378 2.086617 1.400832 C 1.556147 0.361837 3.391246 C -1.183409 -0.587472 -0.758060 C -1.488144 -1.956952 -0.678051 C -2.490056 -2.546990 -1.450568 C -3.212557 -1.763178 -2.350804 C -2.916571 -0.403757 -2.475428 C -1.912183 0.165882 -1.692241 H 1.971237 0.056703 1.326798 H 0.350810 2.304660 1.076943	H = -1.094.904656 G = -1.094.962388

H -0.581122 2.170152 -0.426408 H -2.010684 -0.645918 1.733578 H -1.020426 -0.743778 3.185001 H -1.071890 1.744637 3.408346 H -2.734010 1.194609 3.188698 H -1.962726 3.155152 1.617882 H -2.683461 1.768975 0.800765 H 0.870978 -0.117063 4.093841 H 1.526287 1.446516 3.555227 H 2.565191 0.006314 3.606876 H -2.692464 -3.607752 -1.350822 H -3.992670 -2.217716 -2.953404 H -3.463158 0.213635 -3.181407 H -1.688687 1.219736 -1.812906 Cl -0.574085 -3.017792 0.405548	
TSiso-1a_cat	**B3LYP/6-31+G**** (Hartree)
33 scf done: -1095.184746 C 0.000000 0.000000 0.000000 C 0.000000 0.000000 1.430315 N 1.241517 0.000000 2.046339 O 1.151390 0.334423 -0.570366 C 1.419568 0.343000 3.456778 C -0.677547 1.765071 1.125040 C -1.185684 -0.559762 2.220705 C -1.939086 0.606717 2.886625 C -2.029807 1.685910 1.797768 C -1.107166 -0.473366 -0.877927 C -1.333279 -1.856488 -1.018799 C -2.315295 -2.341462 -1.879840 C -3.081082 -1.442659 -2.624763 C -2.854177 -0.068799 -2.521246 C -1.868446 0.410745 -1.660214 Cl -0.340688 -3.007132 -0.137729 H 2.000986 0.313663 1.454784 H 0.119278 2.221839 1.711943 H -0.669427 2.207640 0.130462 H -0.819695 -1.299628 2.935134 H -1.864148 -1.076806 1.540162 H -2.921041 0.287306 3.245005 H -1.381156 0.986933 3.748679 H -2.805561 1.431684 1.068556 H -2.278471 2.673244 2.207255 H 1.172243 1.389276 3.682096 H 2.467957 0.176306 3.708803 H 0.814184 -0.306044 4.092024 H -2.469280 -3.410752 -1.969605 H -3.847592 -1.822256 -3.292329 H -3.440019 0.630861 -3.107181 H -1.698152 1.479212 -1.591340 H 1.084558 0.383780 -1.539630	H = -1095.325579 G = -1095.383373 

3.6 Conformational study on compound iso-7

Conformations of compound **iso-7** were analyzed by scanning the potential energy surface corresponding to the rotation of the ortho-chlorophenyl group for both (*R*) and (*S*)-stereoisomers. The crystallographic cif file for compound **iso-7** was utilized to build the Z-matrix for the *R*-stereoisomer. The rotation of the o-chlorophenyl group was computed through 20° steps around the $\sigma_{C\text{-}C}$ bond indicated in blue in Figure 1a at the B3LYP/6-31G* level of theory in ethanol (PCM). The relative energy values are indicative.

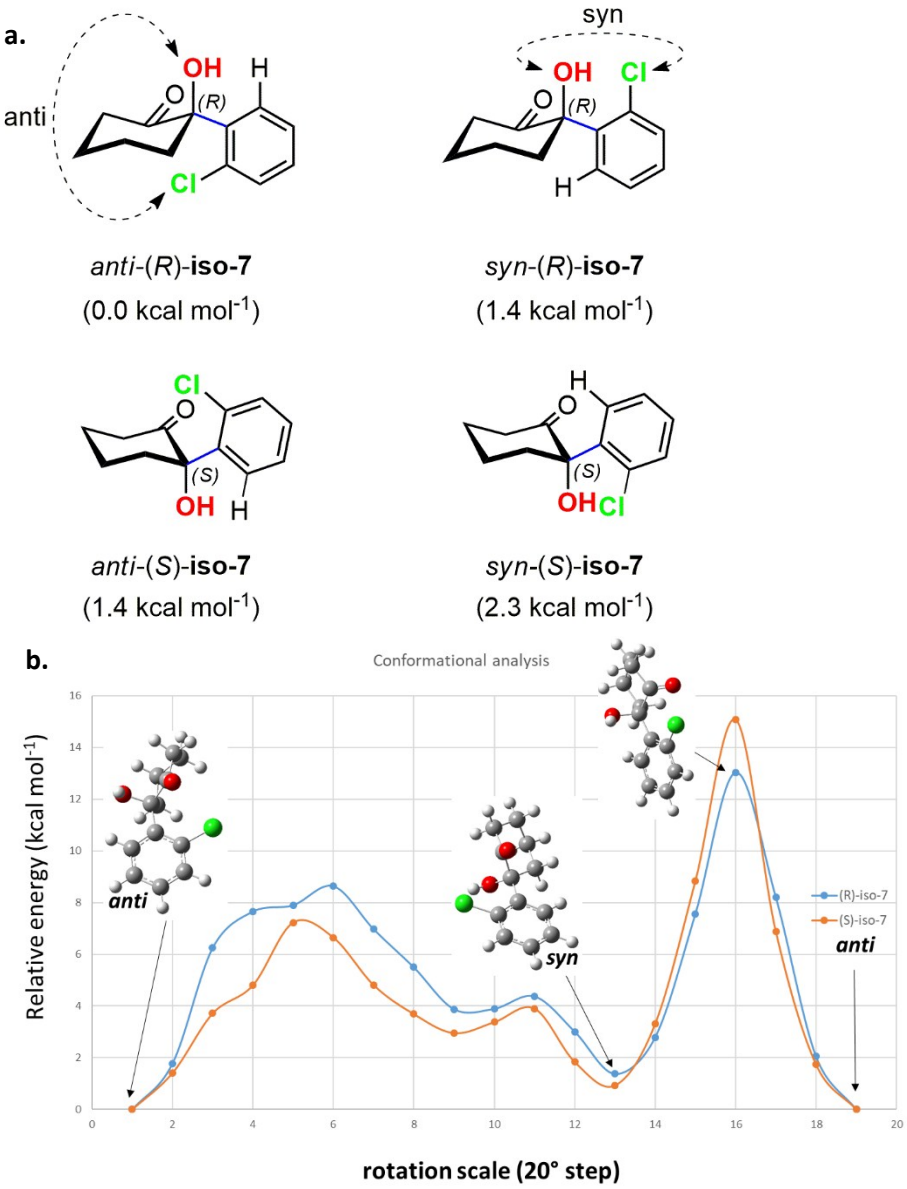


Figure S52. a Relative energies and structures of the four isomers of **iso-7**. *Anti* and *syn* refer to the relative spatial position of the hydroxyl and chloro groups, while the phenyl and the cyclohexyl rings are nearly orthogonal. **b.** Conformational analysis for (*R*)- and (*S*)-**iso-7** (B3LYP/6-31G*, 20° step). Rotation was effected with 20° steps around the $\sigma_{C\text{-}C}$ bond indicated in blue in Figure 1a. Step 19 corresponds to a full 360° rotation for the phenyl ring. Structures are illustrated for (*R*)-**iso-7** only.

Relative energies and structures of the four isomers of **iso-7** are indicated in Figure S52a. Both energy profiles for (*R*)- and (*S*)-**iso-7** stereoisomers are almost superimposable, indicating that both stereoisomers have a preference for the *anti*-conformation (Figure S52b). From the conformational analysis on (*R*)- and (*S*)-**iso-7**, it appeared that two main stable conformers exist: the *anti*- and the *syn*-conformers. The *anti*-conformer is the most stable one for both (*R*)- and *(S)*-**iso-7**, although the computed $\Delta\Delta G°$ between *anti* and *syn*-conformers is only of ~1 kcal.mol^{-1}. For (*R*)-**iso-7**, the *syn* conformer shows the emergence of a stabilizing OH----Cl interaction (H-bond type, 2.34 Å between O—**H** and **Cl**), although the steric hindrance between the ortho' H and the α-methylene position (relative to the stereogenic center on the cyclohexyl fragment) makes it 1.4 kcal mol^{-1} less stable that the *anti*-conformer.

Anti-(*R*)-**iso-7** is the most stable species (*anti*-(*R*)-**iso-7** also corresponds to the structure obtained by X-ray diffraction after recrystallization). Both rotation profiles for (*R*)- and *(S)*-iso-7 show a relatively high calculated rotational barriers of 13-15 kcal mol^{-1} between two conformers when the rotation brings the ketone and chloro substituent in close proximity. With such a value for the rotation barrier, it is expected that *anti*/*syn* rotation is most likely not hampered in solution and the *anti*/*syn*-conformers can thus be considered as stereolabile atropoisomers.

4 References

S1 Y.-F. Liang and N. Jiao, *Angew. Chem. Int. Ed.*, 2014, **53**, 548–552.

S2 B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, 1951, **73**, 2188–2195.

S3 G. A. Shevchenko, S. Dehn and B. List, *Synlett*, 2018, **29**, 2298–2300.

S4 R. F. Parcell and J. P. Sanchez, *J. Org. Chem.*, 1981, **46**, 5055–5060.

S5 Z.-Q. Zhang, T. Chen and F.-M. Zhang, *Org. Lett.*, 2017, **19**, 1124–1127.

S6 P. J. Morris, R. Moaddel, P. Zanos, C. E. Moore, T. Gould, C. A. Zarate Jr. and C. J. Thomas, *Org. Lett.*, 2017, **19**, 4572–4575.

S7 Y. Zhang and O. Ramström, *Chem. Eur. J.*, 2014, **20**, 3288–3291.

S8 *Rigaku Oxford Diffraction, CrysAlis Pro, Rigaku Oxford Diffraction, Yarnton, England, 2015*, .

S9 O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Crystallogr.*, 2009, **42**, 339–341.

S10 G. M. Sheldrick, *Acta Crystallogr.*, 2008, **A64**, 112–122.

S11 G. M. Sheldrick, *Acta Crystallogr.*, 2015, **C71**, 3–8.

S12 G. G. Bizhanova, K. Y. Suponitsky, Y. V Vakhitova and R. R. Gataullin, *Tetrahedron*, 2017, **73**, 109–115.