Supporting Information

A Highly Enantioselective Hydrogenation of Amides via Dynamic Kinetic Resolution Under Low Pressure and Room Temperature

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General Information

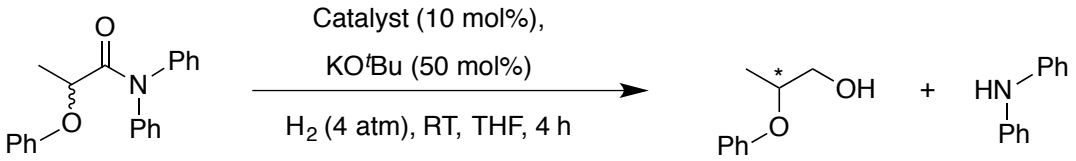
The rapid screening hydrogenation reactions were carried out in a 96-well plate (96 separate glass vials, each equipped with a magnetic stir bar) sealed within a brass reactor block at Center for Catalysis Research and Innovation (CCRI), Ottawa. All of the individual large-scale pressurized reactions were carried out in a stainless steel pressure reactor equipped with a magnetic stir bar at University of Alberta. The solvents tetrahydrofuran (Na/benzophenone), 2-propanol (Mg), methylene chloride (CaH_2) and hexanes (CaH_2) were dried by distillation with the appropriate drying agent under Ar or N_2. Ar or N_2 was bubbled through all solvents for a minimum of 45 min before their use. The 2-bromopropanoic acid, 4-fluorophenol, 4-chlorophenol, 4-bromophenol, 4-methoxyphenol, and 2-phenoxypropionyl chloride were all obtained from Alfa Aesar. The 3-fluorophenol and *α*-bromophenylacetic acid were obtained from TCI. The piperidine, 2,5-norbornadiene, morpholine, potassium *tert*-butoxide, and diisobutylaluminum hydride (1.0 M in toluene) were all obtained from Sigma-Aldrich. The thionyl chloride was obtained from Fluka, the sodium hydride from BDH, and the phenol from EM Science. $LiAlH_4$ was obtained from Anachemia. When possible, the liquid reagents were distilled before use. Table S1 lists the suppliers of the ligands used in this study. The ^{1}H NMR spectra were acquired using both 400 MHz and 500 MHz Varian Inova, and Varian DD2 M2 400 MHz NMR spectrometers. The ^{13}C NMR spectra were acquired using a Varian VNMRS 500 MHz NMR spectrometer. The chemical shifts are reported in parts per million relatives to TMS with the solvent as the internal standard. Abbreviations used in reporting of NMR data are s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), dq (doublet of quartet) and m (multiplet). Elemental Analysis data was acquired with a Carlo Erba EA1108 Elemental Analyzer. Optical rotation data was acquired at 591nm with a Perkin Elmer 241 Polarimeter. HRMS spectra were acquired using either electrospray ionization in an Agilent 6220 ao TOF mass spectrometer or electron ionization on a Kratos Analytical MS50G double focusing sector mass spectrometer. GC-MS analysis was performed by using a Hewlett Packard 5890 chromatograph equipped with a 5970B mass selective detector and Supelco Beta DEX 225 capillary column (30 m × 0.25 mm × 0.25 μm film thickness). HPLC analysis was performed using a Waters 600E multisolvent delivery system equipped with Waters 715 ultra WISP sample processor, Waters temperature control system, Waters 990 photodiode array detector, and a Daicel CHIRALPAK IB (4.6 mm i.d. x 250 mm) chiral column. All of the *ee*'s were confirmed by comparing retention times and mass spectra or UV-Vis data to authentic racemic samples prepared separately.

Table S1. Sources, CAS number, and vial numbers for the ligands used in the rapid screening. Figures S18, S19, S20, and S21 show the structures of these ligands.

Vial	CAS	Supplier	Vial	CAS	Supplier	Vial	CAS	Supplier	Vial	CAS	Supplier
A1			B1	71042-55-2	Strem	C1	96183-46-9	Strem	D1	6737-42-4	TCI
A2	256390-47-3	Strem	B2	610304-81-9	Strem	C2			D2		
A3	505092-86-4	Strem	B3	503538-69-0	Strem	C3	184095-69-0	Solvias	D3	13991-08-7	Strem
A4			B4	866081-62-1	Strem	C4	360048-63-1	Solvias	D4	99646-28-3	Strem
A5	55739-58-7	Strem	B5			C5	292638-88-1	Solvias	D5	76858-94-1	Strem
A6	729572-46-7	Strem	B6	133545-24-1	Strem	C6	166172-63-0	Solvias	D6	137219-86-4	Strem
A7			B7	868851-47-2	Strem	C7	158923-11-6	Solvias	D7	76189-55-4	Strem
A8	917377-74-3	Strem	B8	1020670-88-5	Strem	C8	155830-69-6	Solvias	D8	64896-28-2	Strem
A9	917377-75-4	Strem	B9	244261-66-3	Strem	C9	167416-28-6	Solvias	D9	443150-11-6	Strem
A10	149968-36-5	Strem	B10	145214-57-9	Strem	C10	387868-06-6	Solvias	D10		
A11	255897-36-0	Strem	B11	192463-40-4	Strem	C11			D11	2622-14-2	Aldrich
A12	37002-48-5	Strem	B12	261733-18-0	Strem	C12	77876-39-2	Strem	D12	1259-35-4	Aldrich

Vial	CAS	Supplier	Vial	CAS	Supplier	Vial	CAS	Supplier	Vial	CAS	Supplier
E1	50777-76-9	Strem	F1	10150-27-3	Strem	G1	1086138-36-4	Strem	H1		
E2			F2	1493790-73-0	Strem	G2	338800-13-8	Strem	H2	849923-88-2	Solvias
E3	452304-59-5	Strem	F3		Strem	G3	550373-32-5	Strem	H3	SL-J010-1	Solvias
E4	164858-78-0	Strem	F4	500103-26-4	Strem	G4	851870-89-8	Strem	H4	494227-30-4	Solvias
E5	1237588-12-3	Strem	F5	736158-72-8	Strem	G5	1133149-41-3	Strem			
E6			F6	1150113-66-8	Strem	G6	1101230-28-7	Strem			
E7	422509-53-3	Strem	F7	174758-63-5	Strem	G7	1003012-96-1	Solvias			
E8			F8	208248-67-3	Strem	G8	1357562-70-9	Strem			
E9	799297-44-2	Strem	F9			G9	PNNP (J1)				
E10	192057-60-6	Strem	F10	494227-35-9	Solvias	G10	PNNP (J2)				
E11	960128-64-7	Strem	F11			G11	PP 1 (OP)				
E12	1091606-68-6	Strem	F12		Strem	G12	PP 2 (ONP)				

General Procedure for DKR screening.

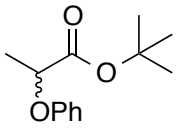
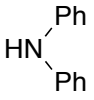
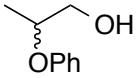
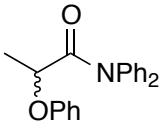
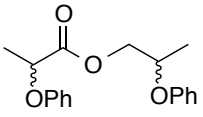


rac-**2**

Between 1.0 and 3.5 mg (2.4-6.2 μmol) of the P, P–P, P–N, P–N–P, and P–N–N–P ligands were weighed into separate wells (vials) of a 96-well plate inside a glove box. Table S1 lists the commercial sources and CAS numbers of the ligands. Figures S18, S19, S20, and S21 show the ligands' structures. A standard solution of (*R,R*)-dpen in THF (50.6 mg in 5.00 mL THF, 0.047 mol L^{-1}) was then added to the vials containing the monophosphines (P, 0.5 equiv dpen per P) and the vials containing the diphosphines (P–P,1 equiv dpen per P–P) ligands. A 0.12 mol L^{-1} solution of catalytic precursor, *cis*-[Ru(η^3-C_3H_5)(MeCN)$_2$(COD)](BF$_4$) (**3**, COD is 1,5-cyclooctadiene) was prepared by dissolving 250.6 mg of **3** in 0.20 ml of CH_2Cl_2 and 4.80 ml of THF. The appropriate amount of this solution was added to each vial (0.5 equiv per P or P–N ligands; and 1 equiv for all other ligands). The 96-well plate was covered and the solutions were heated at 60 °C for 30 min under N_2. The 96-well plate was then allowed to cool to room temperature. A standard solution of KO^{t}Bu, in THF (268.3 mg dissolved in 4.00 mL of THF, 0.6 mol L^{-1}), was then added to each vial (5 equiv) followed by 10 equiv of the substrate, *N,N*-diphenyl-2-phenoxy-propanamide in THF (908.5 mg dissolved in 24.00 mL THF, 0.12 mol L^{-1}). Finally, the appropriate volume of THF was added to each vial to bring the total volume in each vial up to 400 μl. All of the standard solutions and THF were added using Freeslate first-generation core module. The 96-well plate was encased in a brass reactor block, removed from the glove box, and then purged three times by evacuating and backfilling with hydrogen. The hydrogenation reactions were carried out under 4 atm H_2 for 4 h at room temperature. The hydrogenations were halted by depressurizing the reactor and exposing the wells to open air. The reaction products were then analyzed with an Agilent HPLC 1100 system equipped with a DAD detector and a Daicel CHIRALPAK 1B chiral column (4.6 mm i.d. x 250 mm), solvent = 2-PrOH:Hexane 2:98, flow rate = 0.8 mL/min, temperature = 30 °C. The retention times and UV-Vis spectra of the products were confirmed by comparison to those of authentic samples prepared independently. As well, a GC-MS analysis was performed on the products in well D7 to confirm

the identities of diphenylamine, *tert*-butyl 2-phenoxypropanoate, and 2-phenoxypropyl 2-phenoxypropanoate. GC-MS analysis was performed by using an Agilent GC 6890N coupled to an Agilent 5975B MS in EI mode with a CTC GC-PAL autosampler and Agilent HP-5MS ((5% phenyl)-methylpolysiloxane) capillary column, (30 m × 250 μm × 0.25 μm film thickness, He 1.8 mL/min, temperature program of [60 °C held for 3 min.]-[20 °C/min to 175 °C held for 0.25 min]-[25 °C/min to 275 °C held for 0.50 min]-[35 °C/min to 300 °C held for 1.0 min]).

Table S2. HPLC conditions and the retention times of the reactants and products analyzed by HPLC. Retention times are averaged over the chromatograms from the wells.

	Average t_R
	t_R = 5.05 min
	t_R = 9.99 min
	$t_{R(enant.1)}$ = 17.41 min $t_{R(enant.\ 2)}$ = 23.92 min
	$t_{R(enant.\ 1)}$ = 18.51 min $t_{R(enant.\ 2)}$ = 36.16 min
	$t_{R(diast.\ 1)}$ = 8.27 min $t_{R(diast.\ 2)}$ = 8.27 min $t_{R(diast.\ 3)}$ = 25.88 min $t_{R(diast.\ 4)}$ = 44.2 min

Representative UV/Vis spectra of peaks in the HPLC chromatograms from the hydrogenation wells and of control authentic samples.

Figure S1. UV-Vis spectrum obtained from the HPLC chromatogram for the authentic sample of *tert*-butyl 2-phenoxypropanoate. The enantiomers of this compound did not separate under these conditions.

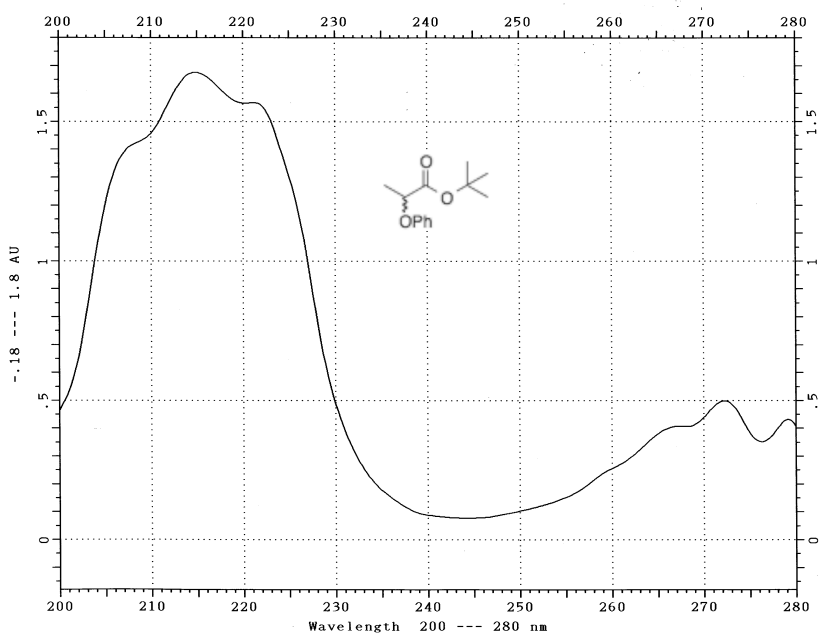


Figure S2. Representative UV-Vis spectrum of *tert*-butyl 2-phenoxypropanoate from the HPLC analysis of the product mixture from hydrogenation carried out during the rapid screening (t_R = 5.05 min).

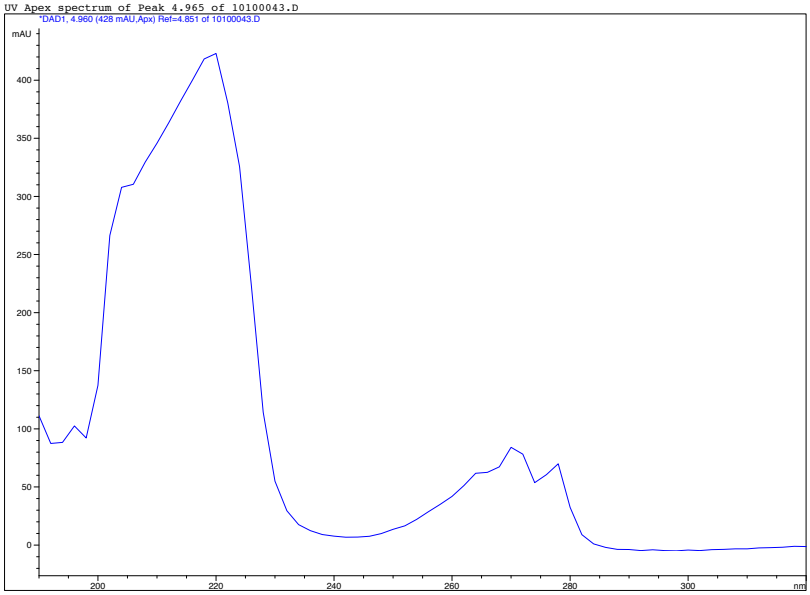


Figure S3. UV-Vis spectrum obtained from the HPLC chromatograph of the authentic sample of diphenylamine.

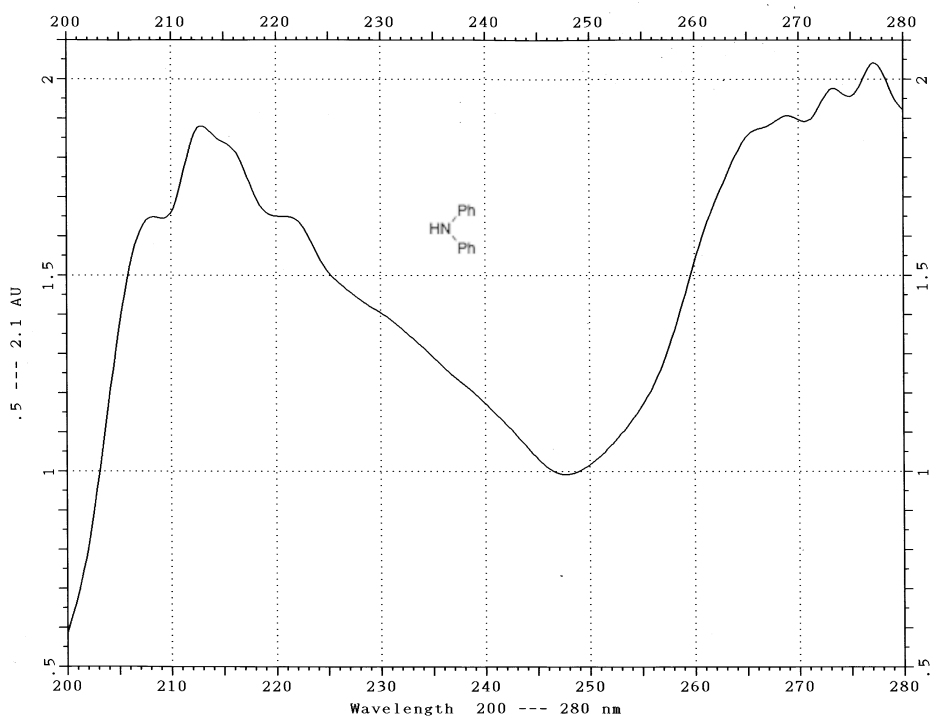


Figure S4. Representative UV-Vis spectrum of diphenylamine from the HPLC analysis of the product mixture from hydrogenations carried out during the rapid screening (t_R = 9.98 min).

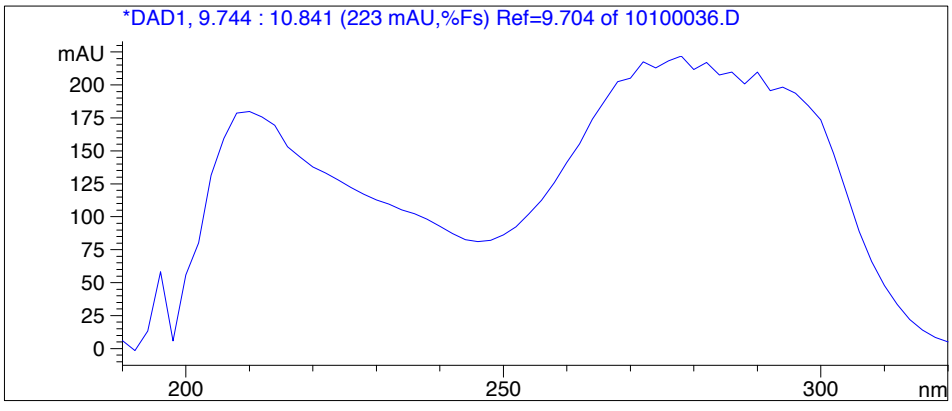


Figure S5. UV-Vis spectrum obtained from the HPLC chromatogram of the authentic sample of *rac*-2-phenoxypropan-1-ol. Both enantiomers are separated.

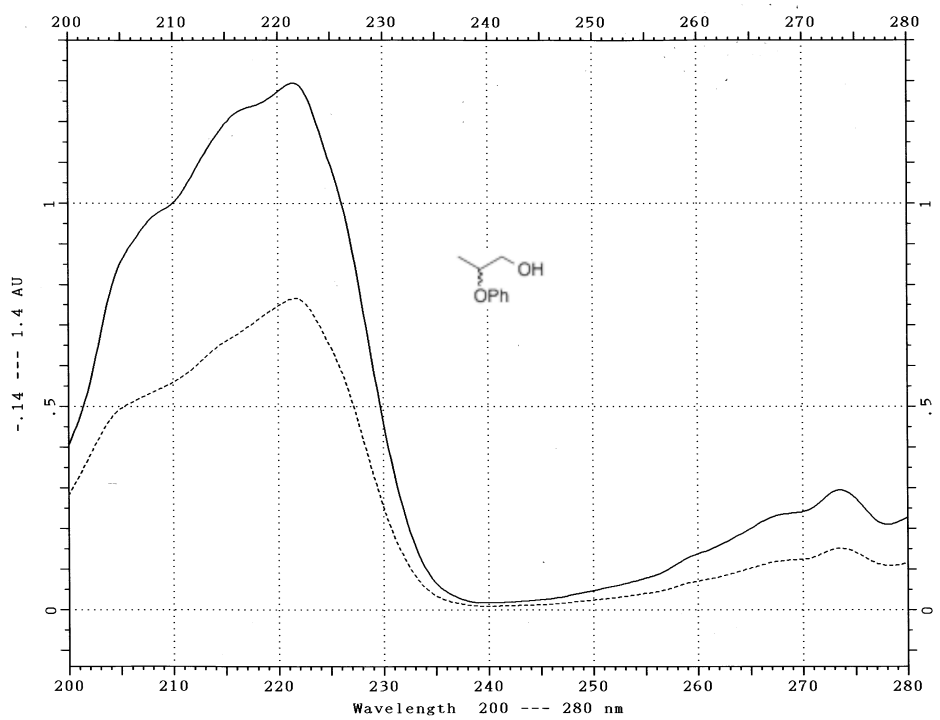


Figure S6. Representative UV-Vis spectrum of both enantiomers of *rac*-2-phenoxypropan-1-ol from HPLC analysis of the product mixture from hydrogenations carried out during the rapid screening (t_R = 17.41 and 23.92 min).

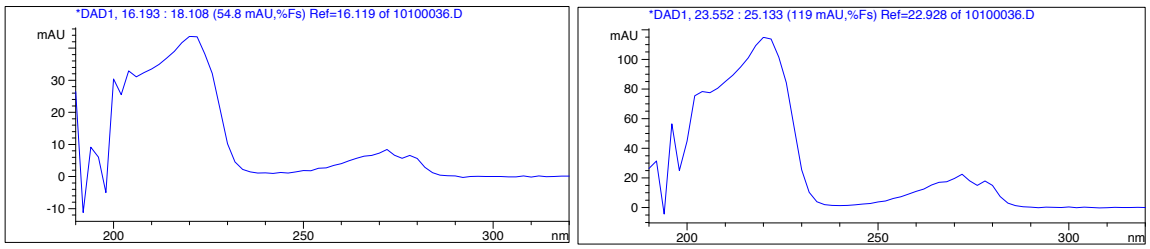


Figure S7. UV-Vis spectrum obtained from the HPLC chromatogram of the authentic sample of *N*,*N*-diphenyl-2-phenoxypropionamide. The spectra of both separated enantiomers are shown.

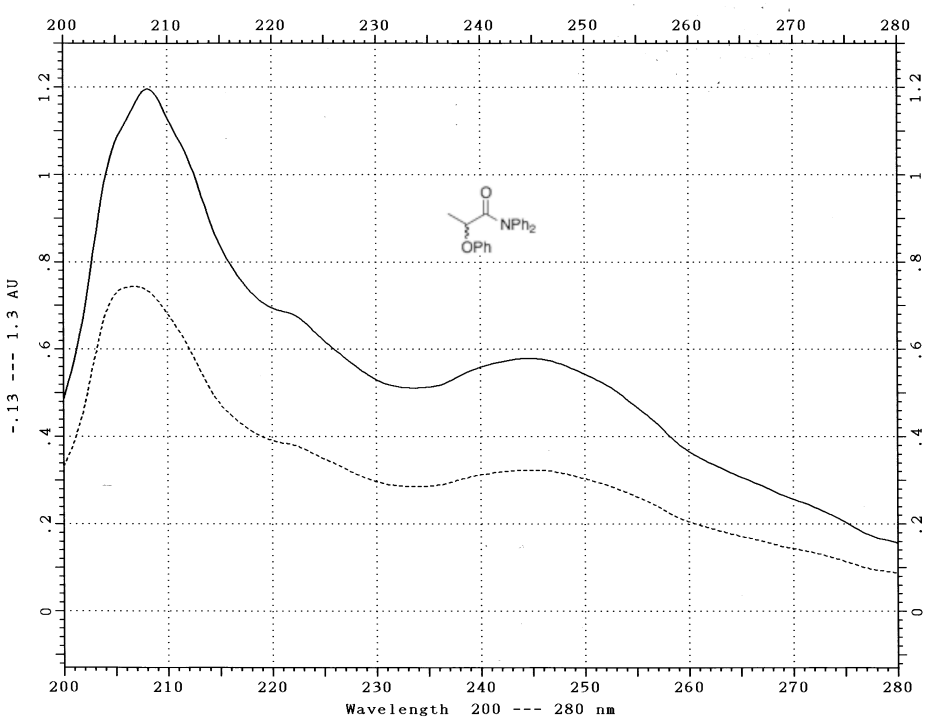


Figure S8. Representative UV-Vis spectrum of *N*,*N*-diphenyl-2-phenoxypropionamide from HPLC analysis of the product mixture from hydrogenations carried out during the rapid screening (t_R = 18.51 and 36.16 min).

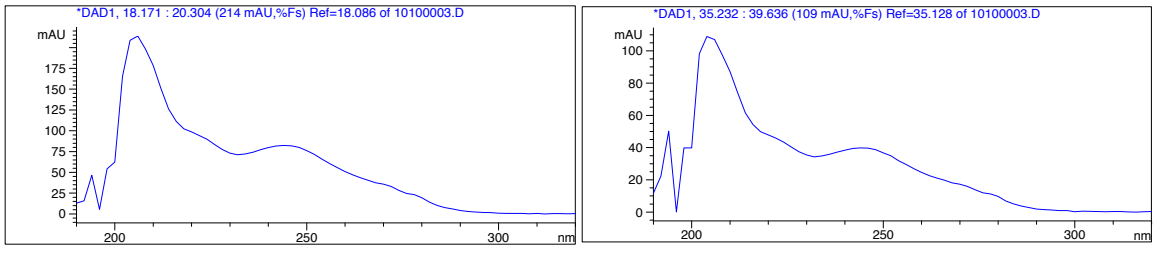


Figure S9. UV-Vis spectrum obtained from the HPLC chromatogram of the authentic sample, 2-phenoxypropyl 2-phenoxypropanoate, showing the three separated diastereomers.

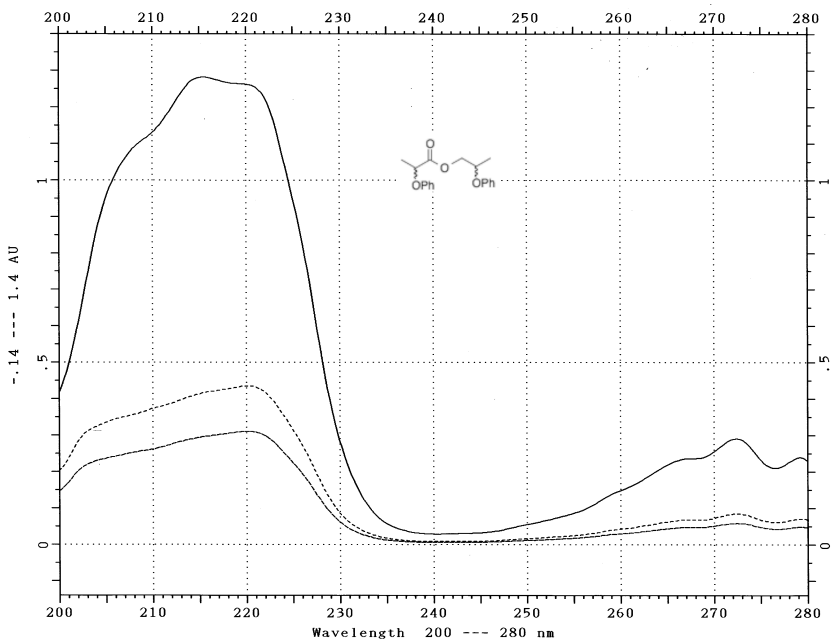
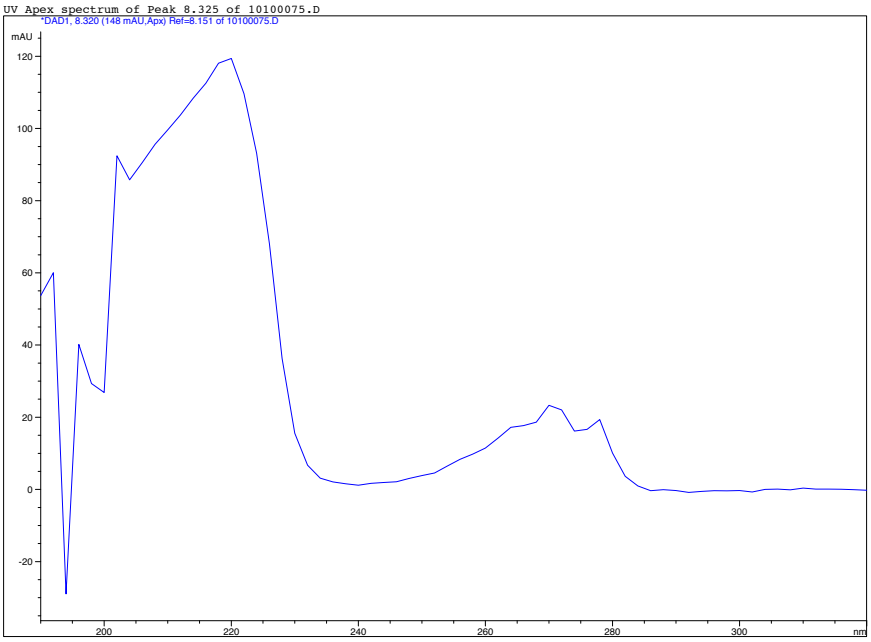


Figure S10. Representative UV-Vis spectrum of the three separated diastereomers of 2-phenoxypropyl 2-phenoxypropanoate from HPLC analysis of the product mixture from hydrogenations carried out during the rapid screening (t_R = 8.27, 25.88, 44.2 min).



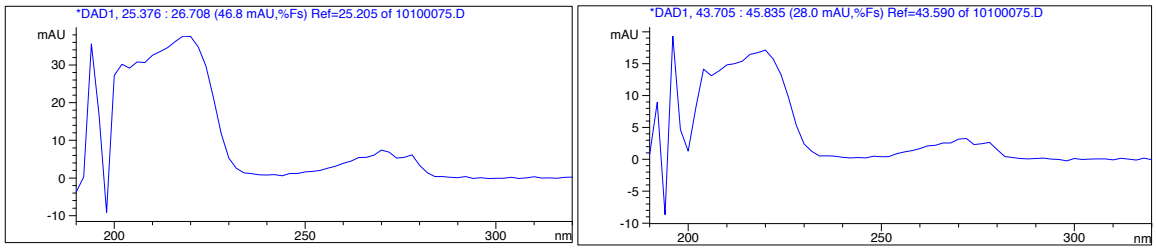


Figure S11. Gas chromatogram of the rapid screening hydrogenation product mixture from reaction well D7.

```
File       :C:\msdchem\1\DATA\Roxanne\1000D7.D
Operator   :
Acquired   : 17 Jun 2013  13:01     using AcqMethod RJune2013.M
Instrument :    Instrument #1
Sample Name:
Misc Info  :
Vial Number: 29
```

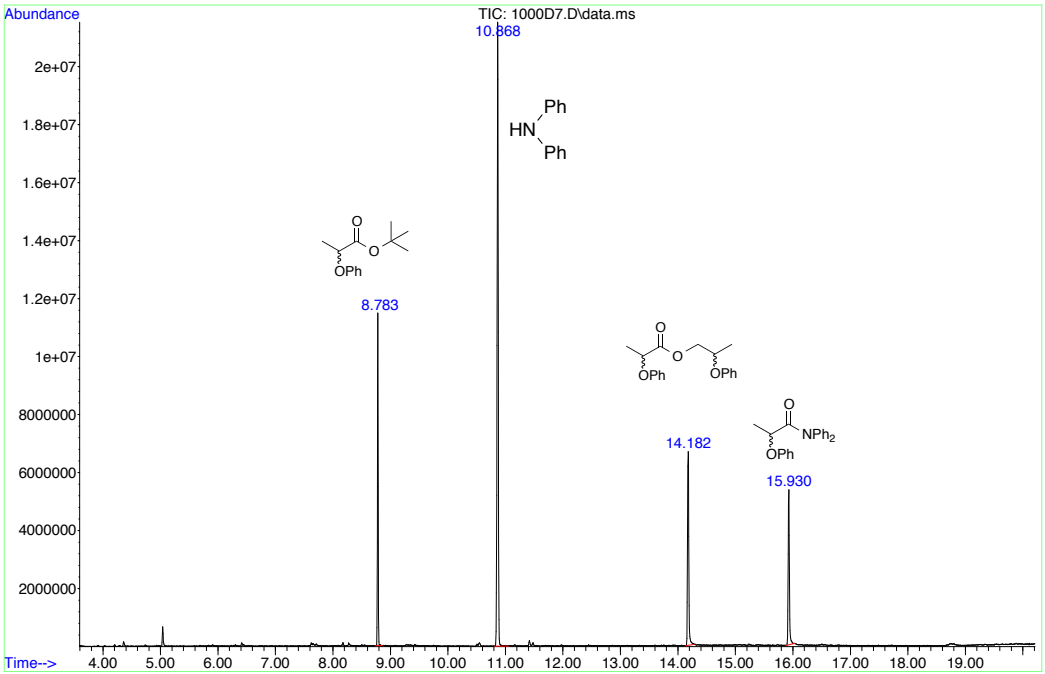


Figure S12. Mass spectrum for the peak at 8.794 min showing the presence of *tert*-butyl 2-phenoxypropanoate in the reaction product mixture.

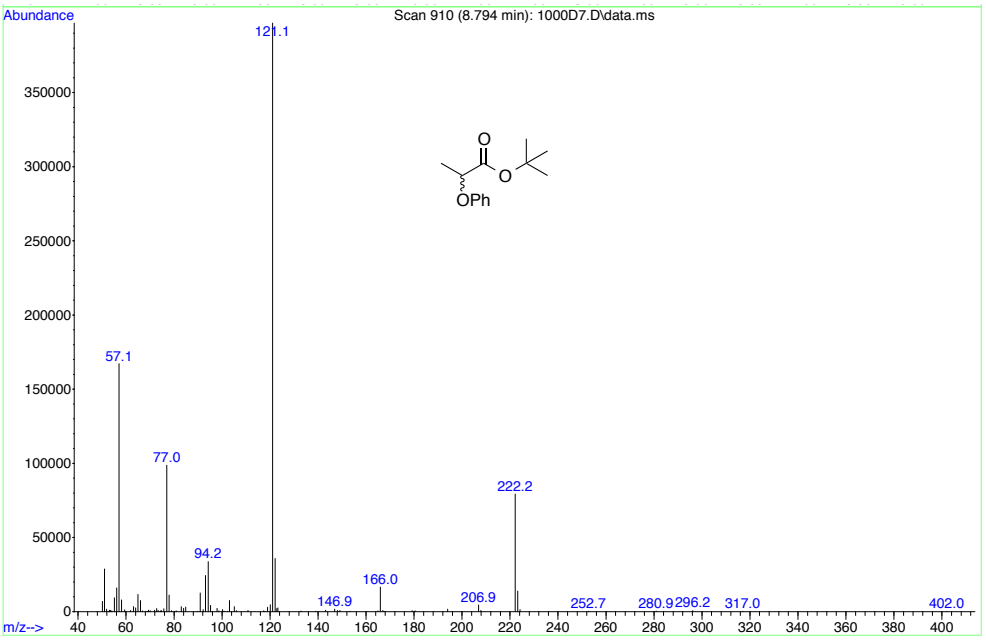
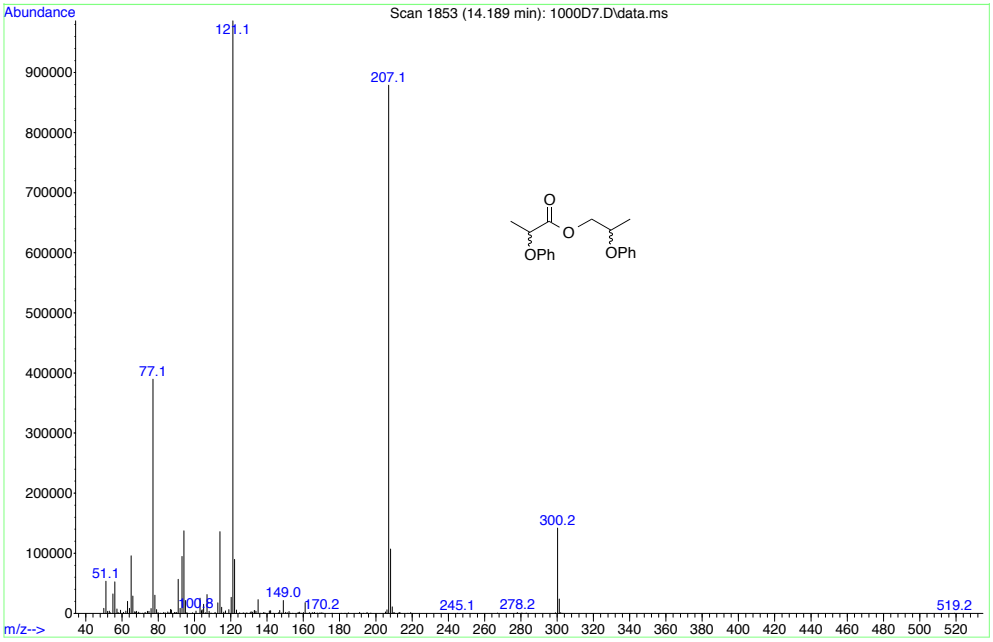


Figure S13. Mass spectrum for the peak at 14.189 min showing the presence of 2-phenoxypropyl 2-phenoxypropanoate in the reaction product mixture.



Representative HPLC chromatograms of the products from the rapid screening.

Figure S14. Representative chromatogram for category I, well A2 ((*R,R*)-dpen and (*R*)-3,4,5-MeO-MeOBIPHEP).

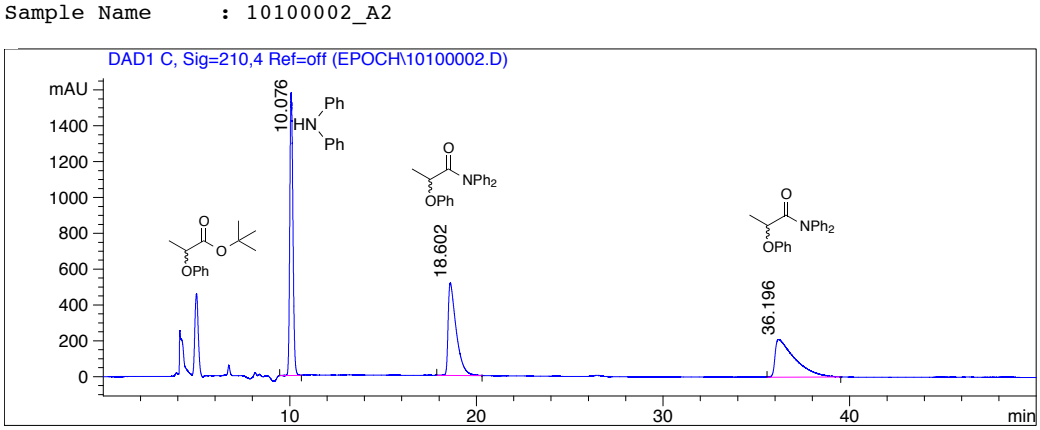


Figure S15. Representative chromatogram for Category II, well D7 ((*R,R*)-dpen and (*R*)-BINAP).

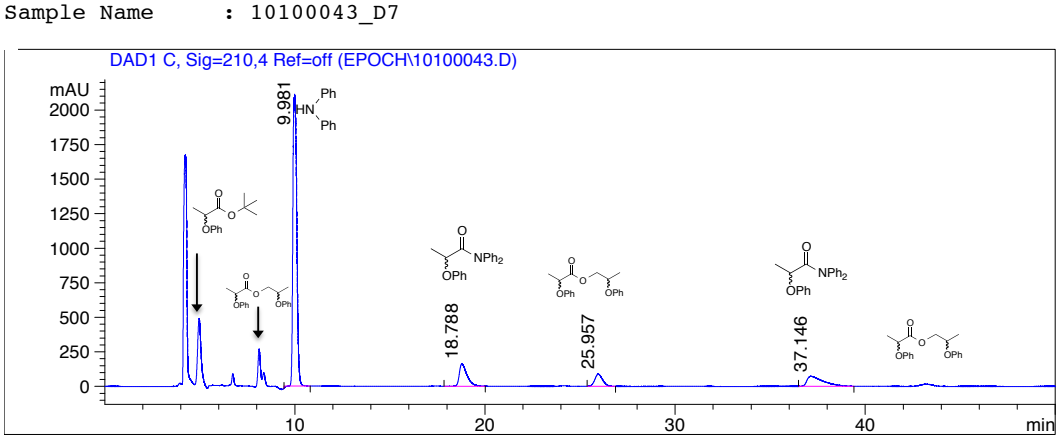


Figure S16. Representative chromatogram for Category III, well G3 (Bis[2-(dicyclohexylphosphino)ethyl]amine).

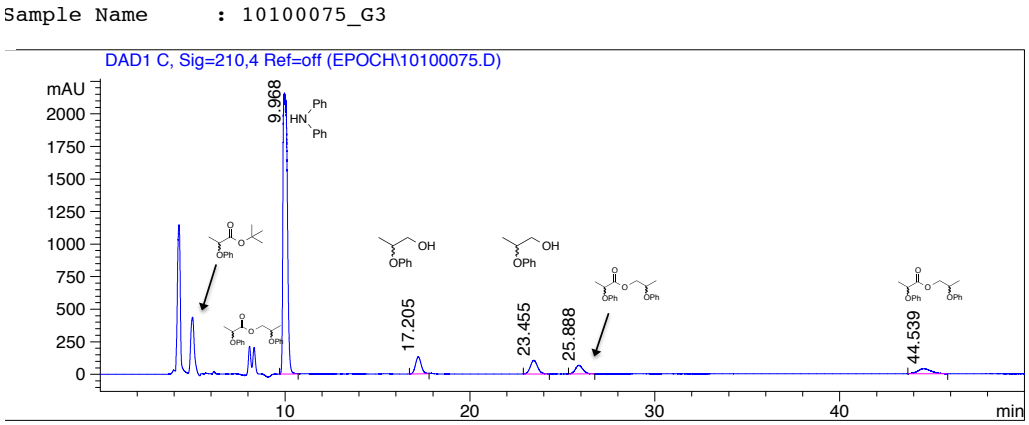
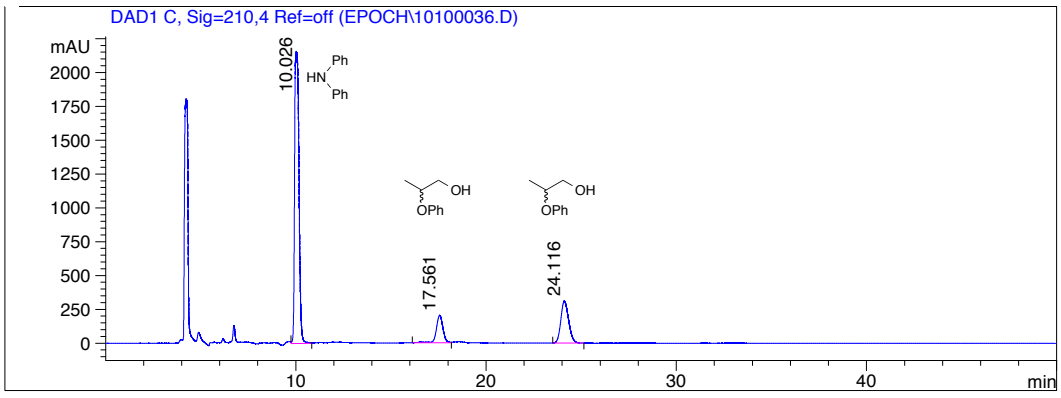


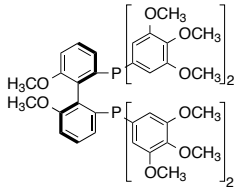
Figure S17. Representative chromatogram for Category IV, well C12 ((*R,R*)-dpen and (*S,S*)-BDPP).



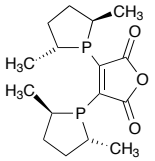
Categorization of ligands based upon their activity in the rapid screening.

I. *Ligands showing little or no activity for the hydrogenation (38 ligands).*
II. *Those with moderate to low amounts of starting materials remaining (12 ligands).*
III. *No starting materials remaining but varying amounts of products and side products (7 ligands).*
IV. *Complete conversion to diphenylamine and 2-phenoxy-1-propanaol (17 ligands).*

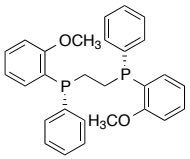
Figure S18. Structures of the ligands in category I.



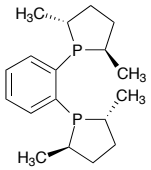
A2, CAS #: 256390-47-3



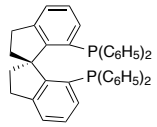
A3, CAS #: 505092-86-4



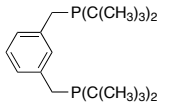
A5, CAS #: 55739-58-7



A7, CAS #: 147253-67-6



A8, CAS #: 917377-74-3



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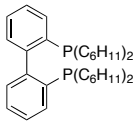

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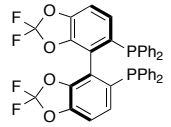

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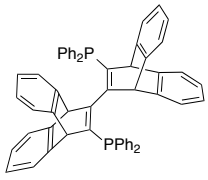
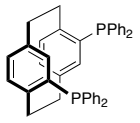


B8, CAS #: 1020670-88-5



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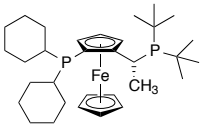

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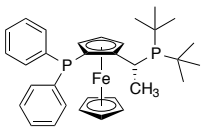
SL-J009-1



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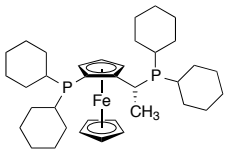
SL-J002-1



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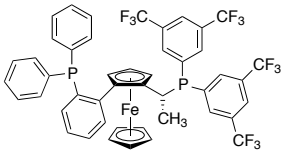
SL-J003-1



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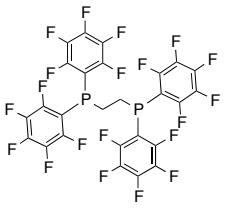
SL-W001-1



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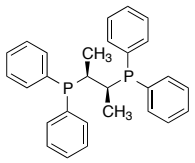

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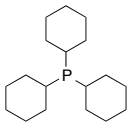

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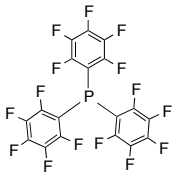

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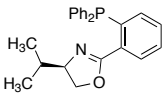

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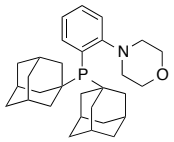

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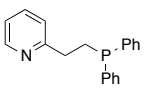
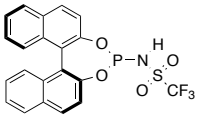
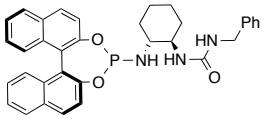


F1, CAS #: 10150-27-3



F2, CAS #: 1493790-73-0



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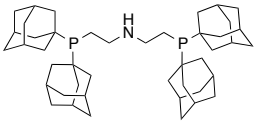
15-2208 (Strem Chemicals)



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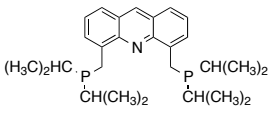

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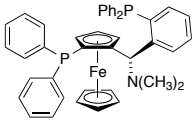
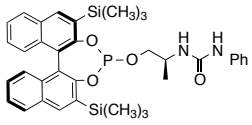
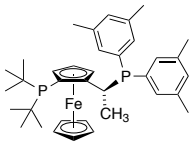


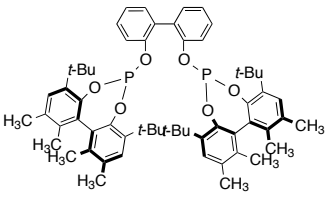
G7, CAS #: 1003012-96-1
SL-T001-1



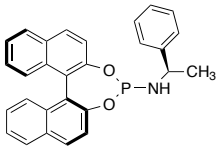
G8, CAS #: 1357562-70-9



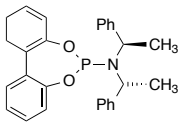
H3, CAS #: ---------
SL-J010-1



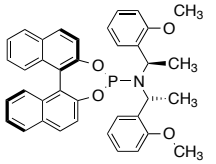
A6, CAS # : 729572-46-7



E7, CAS # : 422509-53-3



F4, CAS # : 500103-26-4



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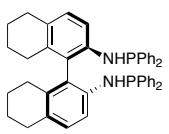

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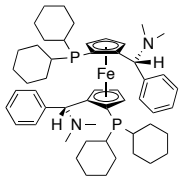
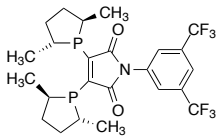


F10, CAS # : 494227-35-9
SL-M002-1



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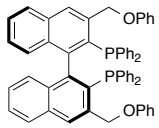
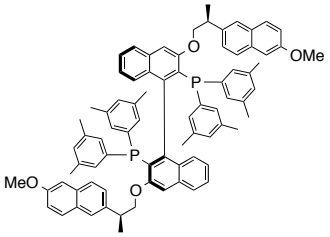
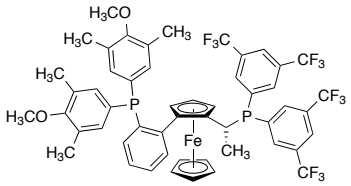


G11, CAS # : XXX

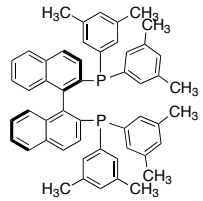


G12, CAS # : XXX

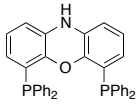


H4, CAS # : 494227-30-4
SL-W005-1

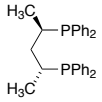
Figure S19. Structures of the ligands in category II.



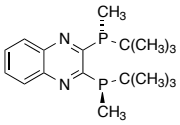
D6, CAS #: 137219-86-4



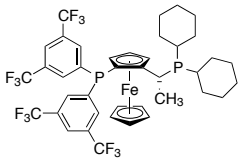
B12, CAS #: 261733-18-0



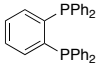
C1, CAS #: 96183-46-9



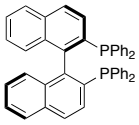
B4, CAS #: 866081-62-1



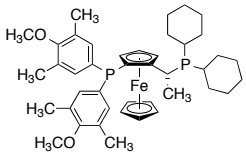
C5, CAS #: 292638-88-1
(SL-J006-1)



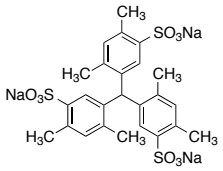
D3, CAS #: 13991-08-7



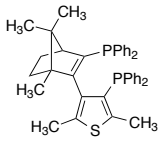
D7, CAS #: 76189-55-4



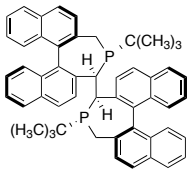
C4, CAS #: 360048-63-1
(SL-J007-1)



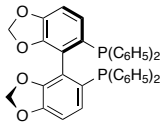
D9, CAS #: 443150-11-6



B7, CAS #: 868851-47-2

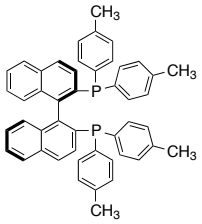


B2, CAS #: 610304-81-9

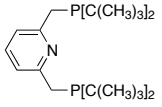


B9, CAS #: 244261-66-3

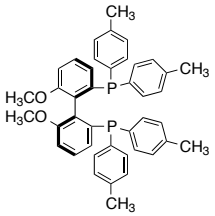
Figure S20. Structures of the ligands in category III.



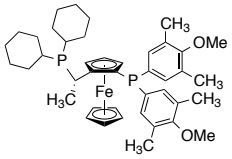
D4, CAS #: 99646-28-3



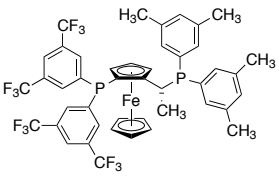
G2, CAS #: 338800-13-8



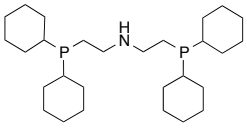
B6, CAS #: 133545-24-1



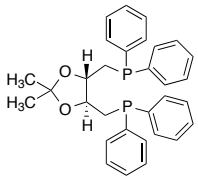
H2, CAS #: 849923-88-2
(SL-J001-5)



C6, CAS #: 166172-63-0
(SL-J008-1)

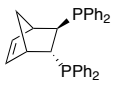


G3, CAS #: 550373-32-5



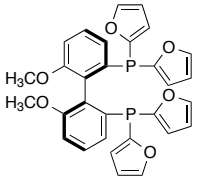
A12, CAS #: 37002-48-5

Figure S21. Structures of the ligands and *ee*'s for the hydrogenations in category IV.



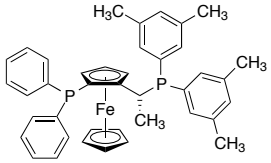
100%, 16.5% *ee*

B1, CAS #: 71042-55-2



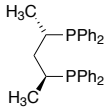
100%, ---% *ee*

B10, CAS #: 145214-57-9



100%, 20.7% *ee*

C3, CAS #: 184095-69-0
SL-J005-1

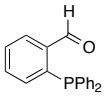


100%, 29.2% *ee*

C12, CAS #: 77876-39-2

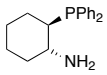
100%, 26% *ee*

D1, CAS #: 6737-42-4



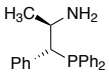
100%, 53.3% *ee*

E1, CAS #: 50777-76-9



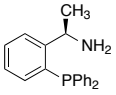
100%, 0.9% *ee*

E3, CAS #: 452304-59-5



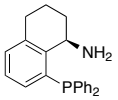
93.8%, 2% *ee*

E9, CAS #: 799297-44-2



100%, 4.2% *ee*

E10, CAS #: 192057-60-6

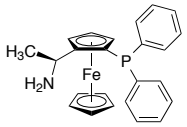


100%, 2.1% *ee*

E11, CAS #: 960128-64-7

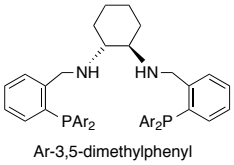
100%, 15.6% *ee*

E12, CAS #: 1091606-68-6



100%, 41.4% *ee*

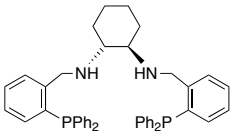
F3, CAS #:NA, 26-1426 (Strem)



Ar-3,5-dimethylphenyl

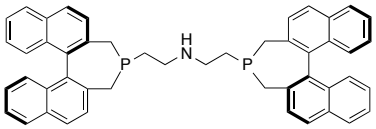
95.6%, 60.2% *ee*

F6, CAS #: 1150113-66-8



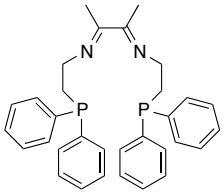
100%, 44.3% *ee*

F7, CAS #: 174758-63-5



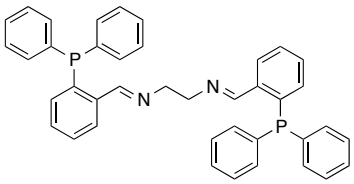
100%, 26.1% *ee*

G4, CAS #: 851870-89-8



100%, 0% *ee*

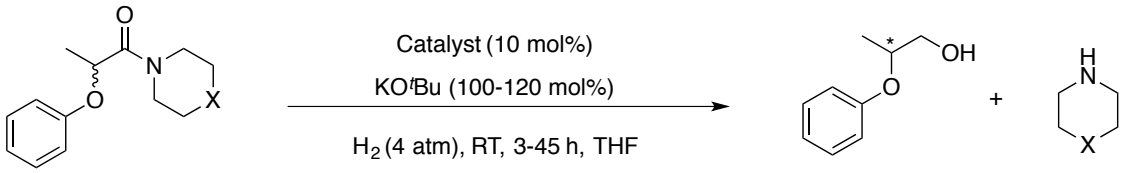
G9, CAS #: 36525-09-4



100%, 0.2% *ee*

G10, CAS #: 74684-87-0

Optimization Experiments



rac - **12** or **13**
rac - **12**, X=O
rac - **13**, X=CH_2

General procedure for *in situ* catalyst preparation in lab-scale hydrogenations.

[Ru(η^3-C_3H_5)(COD)$(MeCN)_2$]BF_4 (**3**, 12.6 mg, 30 μmol), (*S,S*)-skewphos (13.2 mg, 30 μmol), (*R,R*)-dpen (6.4 mg, 30 μmol), and KO^{t}Bu (40.4 mg, 360 μmol, 12 equiv) were weighed into 4 separate NMR tubes inside a glove box. Freshly distilled THF was cannulated into the NMR tubes containing phosphine, diamine ligands (0.3 mL each), and the NMR tube containing base (0.4 mL) under Ar pressure. The THF solution of phosphine was then cannulated into the NMR tube containing the ruthenium precursor under H_2 pressure, followed by the THF solution of the diamine. The resulting solution was allowed to react at 60 °C for 30 min with occasional shaking (at least five times during the heating process). During this time a clear, dark yellow solution formed. After 30 min, the THF solution of KO^{t}Bu was cannulated into the dark yellow solution under H_2 pressure. The mixture turned red in color and was then used for the subsequent hydrogenation.

General procedure for lab-scale hydrogenation (Table 1 of manuscript)

Solid Amide (rac-2-phenoxy-1-(morpholine)-1-propanone (12)):

The amide (70.6 mg, 300 μmol, 10 equiv) was added to the stainless steel autoclave equipped with a stir bar and purged with H_2 for 15-20 min. The prepared catalyst was then transferred to the autoclave under H_2 pressure using a cannula followed by 4.0 mL of freshly distilled THF wash. The autoclave was then sealed and pressurized to 4 atm H_2. The reaction mixture was stirred at room temperature for 3 to 45 hours. The reaction was stopped by depressurizing the autoclave and opening it to air. The catalyst was removed by passing the solution through a florisil plug using CH_2Cl_2 as the rinse solvent. The solvent was then removed under reduced

pressure using a rotary evaporator. The reaction products were analyzed using NMR and GC-MS or HPLC.

Liquid Amide (rac-2-phenoxy-1-(pipyridine)-1-propanone (13))

The stainless steel autoclave was purged with H_2 for 10 min. The amide (69.9 mg, 300 μmol, 10 equiv) in freshly distilled THF (1.0 mL) was cannulated into the autoclave and purged with H_2 for another 10 min. The prepared catalyst was then transferred to the autoclave under H_2 pressure using a cannula followed by 3.0 mL of freshly distilled THF wash. The autoclave was then sealed and pressurized to 4 atm H_2. The reaction mixture was stirred at room temperature for 3.5-21 hours. The reaction was stopped by depressurizing the autoclave and opening it to air. The catalyst was removed by passing the solution through a florisil plug using CH_2Cl_2 as the rinse solvent. The solvent was then removed under reduced pressure using a rotary evaporator. The reaction products were analyzed using NMR and GC-MS or HPLC.

Hydrogenation of 13 with low concentration of base- (Table 1, entry 9)

The reaction was scaled up and performed by following the general procedure; [Ru(η^3-C_3H_5)(COD)$(MeCN)_2$]BF_4 (**3**, 25.2 mg, 60 μmol), (*S,S*)-skewphos (26.3 mg, 60 μmol), (*R,R*)-dpen (12.6 mg, 60 μmol), and KO^{t}Bu (7.4 mg, 66 μmol, 1.1 equiv) and rac-2-phenoxy-1-(pipyridine)-1-propanone (**13**, 143 mg, 600 μmol, 10 equiv). After 20 hours, the reaction was stopped by depressurizing the autoclave and opening it to air. The ^{1}H NMR spectrum ($CDCl_3$) was recorded by taking an aliquot from the reaction mixture (14% conversion by NMR, refer the Figure S24).

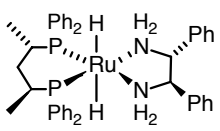
Separation of unreacted starting material.

The reaction mixture was passed through a florisil plug using CH_2Cl_2 (50 mL) as the rinse solvent. The solvent was then removed under reduced pressure using a rotary evaporator to give a reddish oily crude product. The crude product was purified by flash chromatography on a silica column with a 3:1 mixture of hexane:ethyl acetate eluent (Rf=0.12). The enantiomers of 2-phenoxy-1-(pipyridine)-1-propanone were not separated by GC.

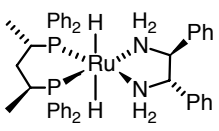
Reduction of isolated 2-phenoxy-1-(pipyridine)-1-propanone with $LiAlH_4$

$LiAlH_4$ (90 mg, 0.8 mmol, 3.1 equiv) was weighed into a side arm flask inside a glove box. Freshly distilled THF (5 mL) was added to the flask under N_2 atmosphere and cooled to 0 °C using an ice bath. The isolated substrate, **13** (60 mg, 0.26 mmol) in THF (5 mL) was then cannulated into the flask containing $LiAlH_4$-THF. The resulting solution was allowed to warm to room temperature and stir overnight. After 16 hours, 2 mL of reaction mixture was transferred to another side arm flask. The reaction mixture was quenched with slow addition of water and stirred for 30 minutes under N_2 atmosphere. The resulting mixture was passed through a celite bed using CH_2Cl_2 (50 mL) as the eluent. The organic solvent was evaporated under reduced pressure. The resulting product was analyzed by both ^1H NMR and GC-MS (Refer the Figures S41 and S45).

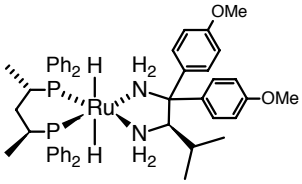
Figure S22. The catalysts used for the optimization experiments (Table 1 of manuscript).



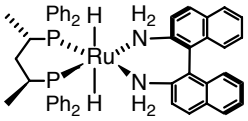
entry1, **7**, 3 h
100%, 25% *ee*



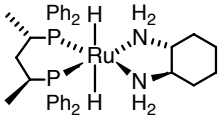
entry 2, **7a**, 16.5 h
100%, 12% *ee*



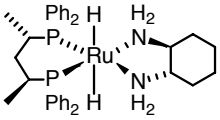
entry 3, **7b**, 42 h
100%, 18% *ee*



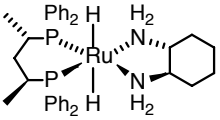
entry 4, **7c**, 16 h
0%, ---% *ee*



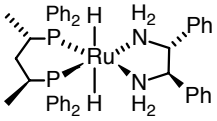
entry 5, **7d**, 45 h
96%, 58% *ee*



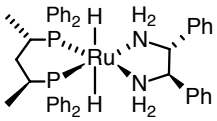
entry 6, **7e**, 41 h
98%, 29% *ee*



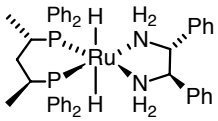
entry 7, **7f**, 21 h
8.3%, 56% *ee*



entry 8, **7**, 3.5 h
96%, 44% *ee*

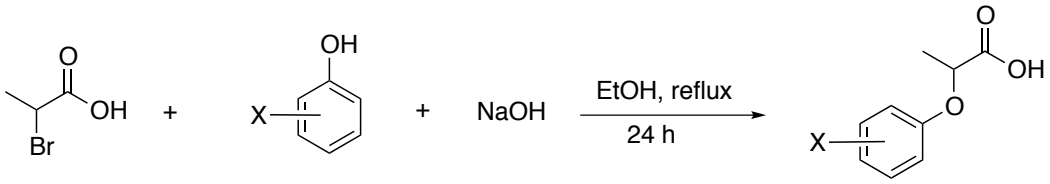


entry 9, **7**, 20 h
25%, 88% *ee*



entry 10, **7**, 24 h
89%, 93% *ee*

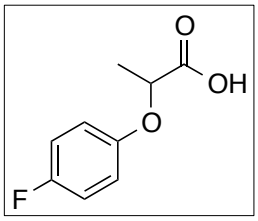
Synthesis of 2-phenoxy acids



General Procedure[1]:

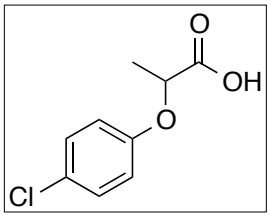
94-111 mmol of phenol or naphthol and 2 equiv of sodium hydroxide were dissolved in 150 mL of absolute ethanol. 1 equiv of 2-bromopropionic acid was then added while stirring vigorously. The mixture was refluxed at 80 °C for 24 hours. After cooling to room temperature, the ethanol was removed under reduced pressure and the resulting solid was dissolved in 150 mL of distilled water and acidified with 6M HCl. The acidified mixture was extracted with 4x60 mL of diethyl ether. The combined ether layers were then extracted with 4x60 mL of saturated aqueous sodium carbonate. The aqueous layers were combined and then acidified with 6M HCl and extracted again with 4x60 mL of ether. The final combined ether layers were washed with brine, then dried over sodium sulfate, and filtered. The solvent was evaporated under reduced pressure to give the crude product.

2-(4-fluorophenoxy)propanoic acid[2] (CAS: 2967-70-6)



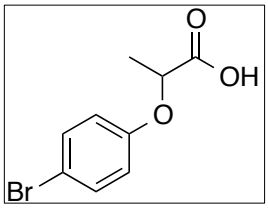
Crude yield 93%, off white powder. **^{1}H NMR** (498.118 MHz, $CDCl_3$, 27.0 °C): δ 1.67 (3H, d, *J*=7.0 Hz, CH_3), 4.75 (1H, q, *J*=6.8 Hz, CH), 6.88 (2H, m, 2 aromatic CH), 7.00 (2H, m, 2 aromatic CH). **^{13}C{^{1}H} NMR** (125.691 MHz, $CDCl_3$, 27.0 °C): δ 18.4 (CH_3), 73.0 (CH), 116.3 (m, aromatic), 153.3 (d, aromatic), 157.0 (aromatic), 158.9 (aromatic), 178.0 (carbonyl). **HRMS (ESI)** m/z Calcd. for $C_9H_8FO_3$ $(M-H)^-$: 183.0463. Found: 183.0461. **EA**: Calcd. for $C_9H_9FO_3$: C 58.70, H 4.93. Found: 58.75, 4.94.

2-(4-chlorophenoxy)propanoic acid[2] (CAS: 3307-39-9)



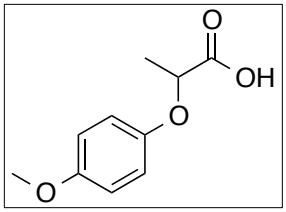
Crude yield 78%, off white powder, purified by crystallization using CH_2Cl_2/Hexane, purified yield 61% white solid. **^{1}H NMR** (399.794 MHz, $CDCl_3$, 26.5 °C): δ 1.68 (3H, d, *J*=6.8 Hz, CH_3), 4.77 (1H, q, *J*=6.8 Hz, CH), 6.85 (2H, d, *J*=8.8 Hz, 2 aromatic CH), 7.26 (2H, d, *J*=9.2 Hz, 2 aromatic CH). **^{13}C{^{1}H} NMR** (125.691 MHz, $CDCl_3$, 27.7 °C): δ 18.4 (CH_3), 72.4 (CH), 116.6 (aromatic), 127.0 (aromatic), 129.6 (aromatic), 155.8 (aromatic), 177.2 (carbonyl). **HRMS (ESI)** m/z Calcd. for $C_9H_9ClO_3$ $(M-H)^-$: 199.0167. Found: 199.0164. **EA**: Calcd. for $C_9H_9ClO_3$: C 53.88, H 4.52. Found: C 54.07, H 4.46.

2-(4-bromophenoxy)-propanoic acid (CAS: 32019-08-2)



Crude yield 90%, off white powder, purified by crystallization using CH_2Cl_2/Hexane, purified yield 79% white solid. **^{1}H NMR** (498.118 MHz, $CDCl_3$, 27.0 °C): δ 1.68 (3H, d, *J*=7.0 Hz, CH_3), 4.77 (1H, q, *J*=7.0 Hz, CH), 6.80 (2H, d, *J*=9.0 Hz, 2 aromatic CH), 7.41 (2H, d, *J*=9.0 Hz, 2 aromatic CH). **^{13}C{^{1}H} NMR** (125.691 MHz, $CDCl_3$, 27.0 °C) δ 18.4 (CH_3), 72.3 (CH), 114.3 (aromatic), 117.0 (aromatic), 132.5 (aromatic), 156.4 (aromatic), 177.7 (carbonyl). **HRMS (ESI)** m/z Calcd. for $C_9H_8BrO_3$ $(M-H)^-$: 242.9662. Found: 242.9659. **EA**: Calcd. for $C_9H_9BrO_3$: C 44.11, H 3.70. Found: C 44.52, H 3.74.

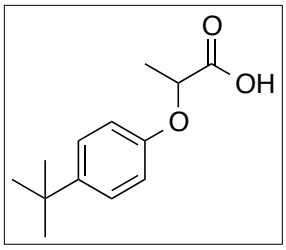
2-(4-methoxyphenoxy)-propanoic acid[3] (CAS: 13794-15-5)



Crude yield 99%, off white powder, purified by crystallization using CH_2Cl_2/Hexane, purified yield 81%, colorless crystals. **^{1}H NMR** (498.118 MHz, $CDCl_3$, 27.0 °C): δ 1.66 (3H, d, *J*=7.0 Hz, CH_3), 3.79 (3H, s, OCH_3), 4.72 (1H, q, *J*=7.0 Hz, CH), 6.86 (4H, m, 4 aromatic CH). **^{13}C{^{1}H} NMR** (125.691 MHz, $CDCl_3$, 27.0 °C): δ 18.4 (CH_3),

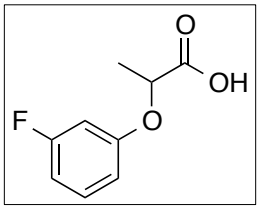
55.7 (CH), 73.3 (CH), 114.8 (aromatic), 116.8 (aromatic), 151.2 (aromatic), 154.8 (aromatic), 177.1 (carbonyl). **HRMS (ESI)** m/z Calcd. for $C_{10}H_{11}O_4$ $(M\text{-}H)^-$: 195.0663. Found: 195.0665. **EA**: Calcd. for $C_{10}H_{12}O_4$: C 61.22, H 6.16. Found: C 61.30, H 6.16.

2-[4-(1,1-dimethylethyl)phenoxy]propanoic acid[4]



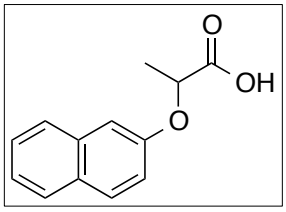
Crude yield 95%, off white powder, purified by crystallization using CH_2Cl_2/Hexane, purified yield 62%, colorless crystals. **^{1}H NMR** (498.118 MHz, $CDCl_3$, 27.0 °C): δ 1.32 (9H, s, $3CH_3$), 1.67 (3H, d, *J*=7.0 Hz, CH_3), 4.79 (1H, q, *J*=6.8 Hz, CH), 6.86 (2H, d, *J*=9.0 Hz, 2 aromatic CH), 7.31 (2H, d, *J*=7.0 Hz, 2 aromatic CH). **^{13}C{^{1}H} NMR** (125.691 MHz, $CDCl_3$, 27.0 °C): δ 18.5 ($C(CH_3)_3$), 31.5 (CH_3), 34.2 (CH_3), 72.3 (CH), 114.7 (aromatic), 126.5 (aromatic), 144.7 (aromatic), 155.0 (aromatic), 178.0 (carbonyl). **HRMS (ESI)** m/z Calcd for $C_{13}H_{17}O_3$: 221.1183. Found: 221.1184. **EA**: Calcd. for $C_{13}H_{18}O_3$ $(M\text{-}H)^-$: C 70.24, H 8.16. Found: C 70.40, H 8.19.

2-(3-fluorophenoxy)-propanoic acid(CAS: 91054-27-2)



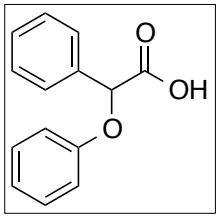
Crude yield 95%, off white powder, purified by crystallization using CH_2Cl_2/Hexane, purified yield 60%, colorless crystals. **^{1}H NMR** (498.118 MHz, $CDCl_3$, 27.0 °C): δ 1.69 (3H, d, *J*=7.0 Hz, CH_3), 4.80 (1H, q, *J*=7.0 Hz, CH), 6.65 (1H, m, aromatic), 6.71 (2H, m, aromatic), 7.27 (1H, m, aromatic). **^{13}C{^{1}H} NMR** (125.691 MHz, $CDCl_3$, 27.0 °C): δ 18.4 (CH_3), 72.2 (CH), 103.2 (d, *J*=25.0 Hz, aromatic), 108.8 (d, *J*=21.4 Hz, aromatic), 110.6 (d, *J*=3.0 Hz, aromatic), 130.5 (d, *J*=9.8 Hz, aromatic), 158.5 (d, *J*=10.8 Hz, aromatic), 163.6 (d, *J*=246.0 Hz, aromatic), 177.9. **HRMS (ESI)** m/z Calcd. for $C_9H_8FO_3$ $(M\text{-}H)^-$: 183.0463. Found: 183.046. **EA**: Calcd. for $C_9H_9FO_3$: C 58.40, H 4.93. Found: C 58.75, H 4.94.

2-(2-naphthalenyloxy)-propanoic acid[5] (CAS: 10470-82-3)



Crude yield 90%, brown powder, purified by crystallization using CH_2Cl_2/Hexane, purified yield 65%, white pink solid. **^{1}H NMR** (498.118 MHz, $CDCl_3$, 27.0 °C): δ 1.75 (3H, d, *J*=6.5 Hz, CH_3), 4.98 (1H, q, *J*=7.0 Hz, CH), 7.12 (1H, d, *J*=2.5 Hz, 1 aromatic CH), 7.23 (1H, dd, *J*=2.5 Hz; *J*=9.0 Hz, 1 aromatic CH), 7.39 (1H, t, *J*=7.2 Hz, 1 aromatic CH), 7.47 (1H, t, *J*=7.0 Hz, 1 aromatic CH), 7.74 (1H, d, *J*=8.5, 1 aromatic CH), 7.80 (2H, d, *J*=9.0 Hz, 2 aromatic CH). **^{13}C{^{1}H} NMR** (125.691 MHz, $CDCl_3$, 27.0 °C): δ 18.5 (CH_3), 72.1 (CH), 107.9 (aromatic), 118.7 (aromatic), 124.2 (aromatic), 126.6 (aromatic), 127.0 (aromatic), 127.7 (aromatic), 129.5 (aromatic), 129.9 (aromatic), 134.2 (aromatic), 155.1 (aromatic), 177.7 (carbonyl). **HRMS (ESI)** m/z Calcd. for $C_{13}H_{11}O_3$ $(M-H)^-$: 215.0714. Found: 215.0715. **EA**: Calcd. for $C_{13}H_{12}O_3$: C 72.21, H 5.59. Found: C 72.20, H 5.57.

2-phenoxy-2-phenylacetic acid (CAS: 3117-38-2)



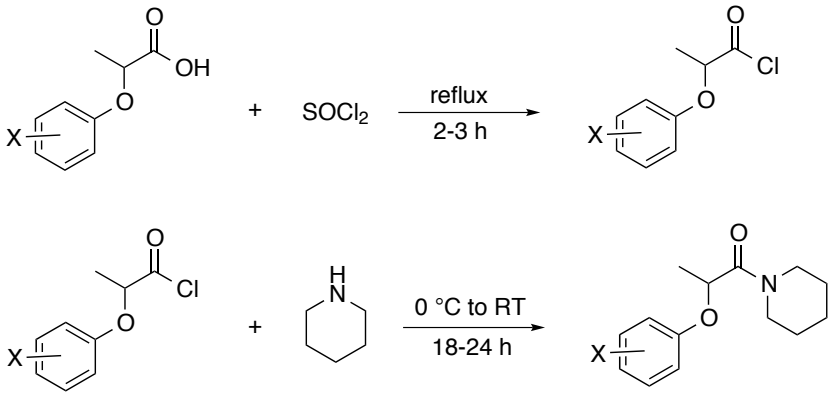
Prepared by a modified version of a literature procedure.[6] A mass of 7.5 g (~35mmol) of *α*-bromophenylacetic acid was converted into an acid chloride (Acid chloride synthesis described later on this SI). The acid chloride was dissolved in 20 ml of DCM, and then freshly distilled 2-propanol (4 equiv) was added dropwise with stirring. The reaction mixture was stirred overnight. The reaction mixture was evaporated under reduced pressure and then dissolved in 50 mL of DCM. The dissolved reaction mixture was then washed with 3x10 mL distilled H_2O, 3x10 mL of saturated aqueous sodium carbonate, and 20 mL of brine. The combined organic layer was then dried over sodium sulfate and filtered. The solvent was evaporated under reduced pressure to yield the isopropyl ester (89%, yellow oil).

The ester (4 g,15.6 mmol) and 1.1 equiv of phenol (1.6 g) were dissolved in 30 mL of distilled THF under N_2 atmosphere. Meanwhile, 1.1 equiv of sodium hydride (0.6 g, 0.6 g/g) weighed into a flask equipped with a stir-bar was immersed into an ice-bath. The resulting THF solution was then transferred slowly into the sodium hydride with stirring. The mixture was then allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched by slowly adding water. The solvent was then removed under reduced pressure and the crude product dissolved in 50 mL of DCM. The mixture was washed with 3x10 mL of distilled H_2O,

3x10 mL of saturated aqueous sodium carbonate, 20 mL of brine, then dried over sodium sulfate, and filtered off. The product was then concentrated *in vacuo* to yield the product (67%, yellowish oil).

The resulting ester (2.8 g) was hydrolyzed by stirring with 10.3 g of NaOH in in 90 mL of distilled H_2O. This mixture was refluxed overnight with stirring. The reaction mixture was then acidified with 6M HCl and then extracted with 4x10 mL DCM. The organic layer was then washed with brine, dried over sodium sulfate, filtered, and then the solvent was evaporated under reduced pressure to yield *α*-phenoxyphenylacetic acid (>99%, off-white solid). **^{1}H NMR** (499.806 MHz, $CDCl_3$, 27.0 °C): δ 5.69 (1H, s, CH), 7.02 (3H, m, 3 aromatic CH), 7.31 (2H, m, 2 aromatic CH), 7.44 (3H, m, 3 aromatic CH), 7.63 (2H, d, *J*=6.5 Hz, 2 aromatic CH). **^{13}C{^{1}H} NMR** (125.691 MHz, $CDCl_3$, 27.0 °C): δ 78.2 (CH), 115.6 (aromatic), 122.1 (aromatic), 127.2 (aromatic), 128.9 (aromatic), 129.3 (aromatic), 129.7 (aromatic), 134.8 (aromatic), 157.0 (aromatic), 175.6 (carbonyl). **HRMS (ESI)** m/z Calcd. for $C_{14}H_{11}O_3$ $(M-H)^-$: 227.0714. Found: 227.0708. **EA**: Calcd. for $C_{14}H_{12}O_3$: C 73.67, H 5.30. Found: C 73.62, H 5.33.

Synthesis of Amides

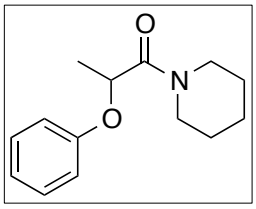


General Procedure:

An acid (19-25 mmol) was placed into a three-neck flask under N_2 atmosphere and dissolved in 6 equiv of thionyl chloride, which was added dropwise while stirring at room temperature. The mixture was refluxed for 2 hours at 74 °C. Excess thionyl chloride was removed using a water aspirator. Any additional thionyl chloride was removed by adding 20 mL of hexanes and removal

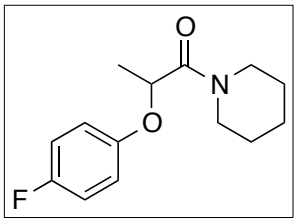
by evaporation using the water aspirator. This hexane extraction was performed 3 times. The resulting acid chloride was dissolved in 30 mL of DCM and cooled to 0 °C. 2.2 molar equiv of piperidine was added at a rate of 1 drop every 3 seconds with vigorous stirring. After addition was completed, the reaction mixture was allowed to warm to room temperature and stirred for 18-24 hours. The reaction mixture was extracted 4 times with water, washed with brine, dried over sodium sulfate and filtered. Finally, the organic solvent was removed under reduced pressure to yield an oily mixture, which was dried under high vacuum for 24 hours.

2-phenoxy-1-(1-piperidinyl)-1-propanone



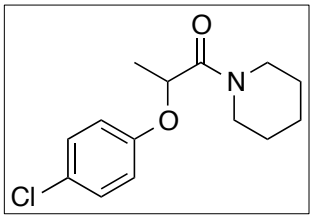
Commercially available acid chloride was used for the synthesis. A viscous yellow-brown oil was obtained from passing the crude product through neutral alumina using CH_2Cl_2 as an eluent, 94% yield. **^{1}H NMR** (499.806 MHz, $CDCl_3$, 27 °C): δ 1.66-1.37 (6H, m, 3 CH_2), 1.63 (3H, d, *J*=7.0 Hz, CH_3), 3.68-3.50 (4H, m, 2 CH_2), 4.98 (1H, q, *J*=6.8 Hz, CH), 6.95 (3H, m, 3 aromatic CH), 7.29 (2H, m, 2 aromatic CH). **^{13}C{^{1}H} NMR** (125.691 MHz, $CDCl_3$, 27 °C): δ 18.0 (CH_3), 24.5 (CH_2), 25.7 (CH_2), 26.5 (CH_2), 43.6 (CH_2), 46.0 (CH_2), 74.4 (CH), 114.9 (aromatic), 121.3 (aromatic), 129.6 (aromatic), 157.4 (aromatic), 169.4 (carbonyl). **HRMS (EI)** m/z: Calcd for $C_{14}H_{19}NO_2$ (M^+, 33.62%) 233.1416; Found 233.1414. 140.1075 (45.69%), 121.0650 (100%), 112.0765 (64.78%), 84.0814 (53.79%).

2-(4-fluorophenoxy)-1-(1-piperidinyl)-1-propanone



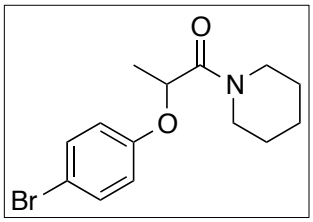
A viscous yellow-brown oil was obtained from passing the crude product through neutral alumina using CH_2Cl_2 as an eluent, 95% yield. **^{1}H NMR** (498.118 MHz, $CDCl_3$, 27 °C): δ 1.39-1.63 (6H, m, 3 CH_2), 1.60 (3H, d, *J* = 6.8 Hz, CH_3), 3.47-3.67 (4H, m, 2 CH_2), 4.90 (1H, m, CH), 6.84-6.87 (2H, m, 2 aromatic CH), 6.95-6.98 (2H, m, 2 aromatic CH). **^{13}C{^{1}H} NMR** (125.691 MHz, $CDCl_3$, 27 °C): δ 18.0 (CH), 24.5 (CH), 25.7 (CH), 26.5 (CH), 43.6 (CH), 46.0 (CH), 75.0 (CH) 115.9 (aromatic), 153.5 (aromatic), 156.6 (aromatic), 158.5 (aromatic), 169.3 (carbonyl). **HRMS (EI)** m/z: Calcd for $C_{14}H_{18}NO_2F$ (M^+, 50.47%) 251.1322; Found 251.1328. 140.1071 (81.24%), (70.56%), 112.0762 (90.03%), 84.0811 (100%), 69.0704 (56.15%).

2-(4-chlorophenoxy)-1-(1-piperidinyl)-1-propanone



A yellow brown oil that solidified to give a tan solid over the course of one week, 57% yield. **^{1}H NMR** (498.118 MHz, $CDCl_3$, 27 °C): δ 1.38-1.64 (6H, m, 3 CH_2), 1.62 (3H, d, *J* = 6.8 Hz, CH_3), 3.48-3.65 (4H, m, 2 CH_2), 4.92 (1H, q, *J*=6.8 Hz CH), 6.85 (2H, d, *J*=9.1 Hz 2 aromatic CH), 7.23 (2H, d, *J*=9.1 Hz, 2 aromatic CH). **^{13}C{^{1}H} NMR** (125.691 MHz, $CDCl_3$, 27 °C): δ 18.0 (CH), 24.5 (CH), 25.7 (CH), 26.5 (CH), 43.6 (CH), 46.0 (CH), 74.8 (CH) 116.1 (aromatic), 126.2 (aromatic), 129.5 (aromatic), 156.1 (aromatic), 169.0 (carbonyl). **HRMS (EI)** m/z: Calcd for $C_{14}H_{18}{}^{35}ClNO_2$ (M^+, 45.31%) 267.1026; Found 267.1021. 140.1069 (83.33%), 128.0021 (45.07%), 112.0775 (74.74%), 84.0813 (100%). **EA**: Calcd. for $C_{14}H_{18}ClNO_2$: C 62.80, H 6.78, N 5.23. Found: C 62.53, H 6.81, N 5.32.

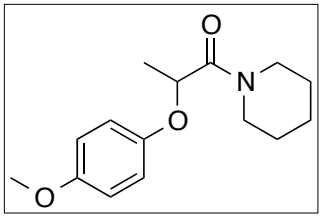
2-(4-bromophenoxy)-1-(1-piperidinyl)-1-propanone



Brown solid, crude yield 95%, purified by flash chromatography on a silica column with 1:2.5 hexane:ethyl acetate as eluent (R_f=0.52). Isolated, purified yield: 47%, white solid.

^{1}H NMR (498.118 MHz, $CDCl_3$, 27.0 °C): δ 1.36-1.74 (6H, m, 3 CH_2), 1.61 (3H, d, *J*=6.5 Hz, CH_3), 3.47-3.65 (4H, m, 2CH_2), 4.96 (1H, q, *J*=6.8 Hz, CH), 6.80 (2H, d, *J*=9.0 Hz, 2 aromatic CH), 7.37 (2H, d, *J*=9.0 Hz, 2 aromatic CH). **^{13}C{^{1}H} NMR** (125.691 MHz, $CDCl_3$, 27.0 °C): δ 18.0 (CH_3), 24.5 (CH_2), 25.7 (CH_2), 26.5 (CH_2), 43.7 (CH_2), 46.0 (CH_2), 74.7 (CH), 113.6 (aromatic), 116.7 (aromatic), 132.4 (aromatic), 156.6 (aromatic), 169.0 (carbonyl). **HRMS (EI)** m/z: Calcd. for $C_{14}H_{18}O_2N^{81}Br$ (M^+, 18.27%) 313.0501; Found 313.0502. Calcd. for $C_{14}H_{18}O_2N^{79}Br$ (M^+, 18.92%) 311.0521; Found 311.0515, 140.1073 (100%), 112.1126 (55.51%), 112.0761 (84.79%), 84.0811 (92.97%). **EA**: Calcd. for $C_{14}H_{18}BrNO_2$: C 53.86, H 5.81, N 4.49. Found: C 53.95, H 5.84, N 5.51.

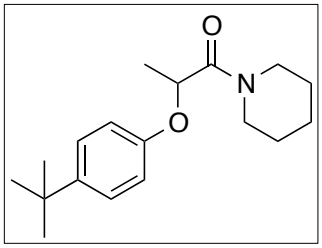
2-(4-methoxyphenoxy)-1-(1-piperidinyl)-1-propanone



Brown solid, 79% crude yield. Purified twice by flash chromatography on a silica column with 1:2.5 hexane:ethyl acetate eluent (R_f=0.57). Isolated, purified yield: 21%. Off white solid.

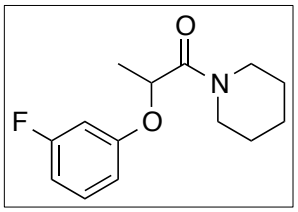
^{1}H NMR (498.118 MHz, $CDCl_3$, 27.0 °C): δ 1.36-1.64 (6H, m, 3 CH_2), 1.59 (3H, d, *J*=7.0 Hz, CH_3), 3.48-3.68 (4H, m, 2CH_2), 3.77 (3H, s, CH_3), 4.89 (1H, q, *J*=6.8 Hz, CH), 6.84 (4H, m, 4 aromatic CH). **^{13}C{^{1}H} NMR** (125.691 MHz, $CDCl_3$, 27.0 °C): δ 18.1 (CH_3), 24.5 (CH_3), 25.7 (CH_2), 26.5 (CH_2), 43.6 (CH_2), 46.0 (CH_2), 55.7 (CH_2), 74.9 (CH), 114.7 (aromatic), 115.9 (aromatic), 151.5 (aromatic), 154.2 (aromatic), 169.6 (carbonyl). HRMS **(ESI^{+})** m/z: Calcd. for $C_{15}H_{22}NO_3$ $(M+H)^+$ 264.1594; Found 264.1594. **EA:** Calcd. for $C_{15}H_{21}NO_3$: C 68.42, H 8.04, N 5.32. Found C 68.51, H 8.04, N 5.43.

2-[4-(1,1-dimethylethyl)phenoxy]-1-(1-piperidinyl)-1-propanone



Light brown solid, crude yield 81.7%, purified by recrystallization from CH_2Cl_2/Hexane, off white solid. **^{1}H NMR** (498.118 MHz, $CDCl_3$, 27.0 °C): δ 1.30 (9H, s, 3CH_3), 1.41-1.67 (6H, m, 3 CH_2), 1.60 (3H, d, *J*=6.5 Hz, CH_3), 3.49-3.65 (4H, m, 2CH_2), 4.95 (1H, q, *J*=6.6 Hz, CH), 6.84 (2H, d, *J*=9.0 Hz, 2 aromatic CH), 7.29 (2H, d, *J*=8.5 Hz, 2 aromatic CH). **^{13}C{^{1}H} NMR** (125.691 MHz, $CDCl_3$, 27.0 °C): δ 18.0 ($C(CH_3)_3$), 24.6 (CH_3), 25.7 (CH_2), 26.5 (CH_2), 31.5 (CH_3), 34.1 (CH_2), 43.6 (CH_2), 46.0 (CH_2), 74.1 (CH), 114.3 (aromatic), 126.3 (aromatic), 144.0 (aromatic), 155.2 (aromatic), 169.6 (carbonyl). **HRMS (EI)** m/z: Calcd. for $C_{18}H_{27}O_2N$ (M^+, 34.60%) 289.2042; Found 289.2039. 177.1279 (60.73%), 140.1074 (98.40%), 112.1127 (39.31%), 112.0762 (38.62%), 84.0809 (100%). **EA**: Calcd. for $C_{18}H_{27}NO_2$: C 74.70, H 9.40, N 4.84. Found: C 74.63, H 9.49, N 4.96.

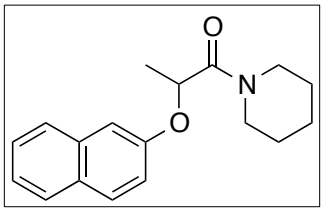
2-(3-fluorophenoxy)-1-(1-piperidinyl)-1-propanone



A pale yellow oil that solidified into a tan solid over the course of a week, 86% yield. **^{1}H NMR** (498.118 MHz, $CDCl_3$, 27.0 °C): δ 1.39-1.67 (6H, m, 3 CH_2), 1.62 (3H, d, *J*=6.5 Hz, CH_3), 3.50-3.65 (4H, m, 2CH_2), 4.95 (1H, q, *J*=6.8 Hz, CH), 6.62-6.71 (3H, m, 3 aromatic CH), 7.22 (1H, m, aromatic CH). **^{13}C{^{1}H} NMR** (125.691 MHz, $CDCl_3$, 27.0 °C): δ 17.9 (CH_3), 24.5 (CH_2), 25.7 (CH_2), 26.5 (CH_2), 43.6 (CH_2), 46.1 (CH_2), 74.5 (CH), 102.8 (d, *J*=24.9Hz, aromatic), 108.2 (d, *J*=24.1Hz, aromatic), 110.4 (aromatic), 130.4 (d, *J*=10.1Hz, aromatic), 158.8 (d, *J*=10.7Hz, aromatic), 163.6 (d, *J*=245.5Hz, aromatic), 168.9

(carbonyl). **HRMS (EI)** m/z: Calcd for $C_{14}H_{18}O_2NF$ (M^+, 36.01%) 251.1322; Found 251.1322. 140.1068 (31.56%), 139.0553 (41.92%), 112.0758 (100%), 84.0811 (44.24%), 69.0685 (41.55%). **EA**: Calcd. for $C_{14}H_{18}FNO_2$: C 66.91, H 7.22, N 5.57. Found: C 67.00, H 7.27, N 5.70

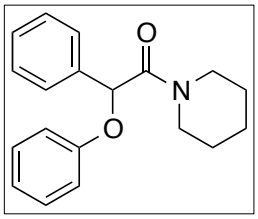
2-(2-naphthalenyloxy)-1-(1-piperidinyl)-1-propanone



Brown solid, 96% crude yield. Purified by flash chromatography on a silica column with a 1:2.5 mixture of hexane:ethyl acetate eluent (R_f=0.55), off white solid.

^{1}H NMR (498.118 MHz, $CDCl_3$, 27.0 °C): δ 1.36-1.74 (6H, m, 3 CH_2), 1.69 (3H, d, *J*=7.0 Hz, CH_3), 3.54-3.70 (4H, m, $2CH_2$), 5.13 (1H, q, *J*=6.6 Hz, CH), 7.19 (2H, m, 2 aromatic CH), 7.36 (1H, m, aromatic CH), 7.45 (1H, m, aromatic CH), 7.74-7.79 (3H, m, aromatic CH). **^{13}C{^{1}H} NMR** (125.691 MHz, $CDCl_3$, 27.0 °C): δ 18.0 (CH_3), 24.5 (CH_2), 25.7 (CH_2), 26.5 (CH_2), 43.7 (CH_2), 46.1 (CH_2), 74.5 (CH), 107.6 (aromatic), 118.7 (aromatic), 123.9 (aromatic), 126.4 (aromatic), 127.0 (aromatic), 127.6 (aromatic), 129.2 (aromatic), 129.7 (aromatic), 134.5 (aromatic), 155.4 (aromatic), 169.3 (carbonyl). **HRMS (EI)** m/z: Calcd for $C_{18}H_{21}O_2N$ (M^+, 21.67%) 283.1572; Found 283.1570. 112.1126 (43.21%), 112.0760 (33.84%), 62.0171 (100%). **EA**: Calcd. for $C_{18}H_{21}NO_2$: C 76.29, H 7.47, N 4.94. Found: C 76.06, H 7.48, N 5.00.

2-phenoxy-2-phenyl-1-(1-piperidinyl)-ethanone

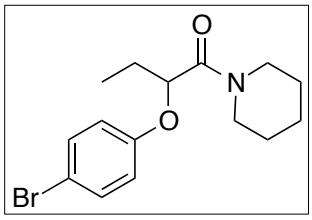


Product was purified by flash chromatography on a silica column with a 50:1 ratio of silica to product, 4:1 hexane:ethyl acetate eluent, R_f of 0.27. Product was dissolved in a minimum volume of DCM before injecting onto column. Purified yield, 88%, white solid.

^{1}H NMR (499.806 MHz, $CDCl_3$, 27.0 °C): δ 1.21-1.86 (6H, m, 3 CH_2), 3.40-3.61 (4H, m, 2 CH_2), 5.96 (1H, s, CH), 7.05 (3H, m, 3 aromatic CH), 7.38 (5H, m, 5 aromatic CH), 7.59 (2H, m, 2 aromatic CH). **^{13}C{^{1}H} NMR** (125.691 MHz, $CDCl_3$, 27.0 °C): δ 24.4 (CH_2), 25.6 (CH_2), 25.8 (CH_2), 43.8 (CH_2), 46.2 (CH_2), 80.7 (CH), 115.3 (aromatic), 121.7 (aromatic), 126.0 (aromatic), 128.2 (aromatic), 128.7 (aromatic), 129.7 (aromatic), 136.1 (aromatic), 157.8 (aromatic), 167.7 (carbonyl). **HRMS (EI)** m/z: Calcd. for $C_{19}H_{21}NO_2$ (M^+,

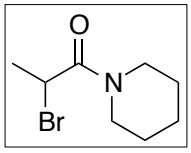
7.98%) 295.1572; Found 295.1568. 183.0808 (100%), 174.1287 (31.88%), 77.0383 (20.32%), 69.0700 (18.62%). **EA**: Calcd. for $C_{19}H_{21}NO_2$: C 77.26, H 7.17, N 4.74. Found: C 76.57, H 7.18, N 4.73.

2-(4-bromophenoxy)-1-(1-piperidinyl)-1-butanone



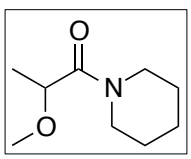
Viscous yellow-brown oil was obtained from passing the crude product through neutral alumina using CH_2Cl_2 as an eluent. 66% yield. **^{1}H NMR** (498.118 MHz, $CDCl_3$, 27.0 °C): δ 1.10-1.13 (3H, t, *J*=7.5 Hz, CH_3), 1.59-1.62 (6H, m, 3 CH_2), 1.96-1.99 (2H, m, *J*=6.5 Hz, CH_2), 3.42-3.70 (4H, m, 2CH_2), 4.65-4.68 (1H, m, CH), 6.82 (2H, d, *J*=7.0 Hz, 2 aromatic CH), 7.37 (2H, d, *J*=9.0 Hz, 2 aromatic CH). **C{^{1}H} NMR** (125.691 MHz, $CDCl_3$, 27.0 °C): δ 10.4 (CH_3) 24.5.0 (CH_3), 25.8 (CH_2), 26.5 (CH_2), 26.5 (CH_2), 43.7 (CH_2), 46.0 (CH_2), 80.9 (CH), 113.6 (aromatic), 116.7 (aromatic), 132.4 (aromatic), 157.1 (aromatic), 169.0 (carbonyl). **HRMS (ESI)** m/z Calcd. for $C_{15}H_{21}BrNO_2$ $(M+H)^+$: 326.0750. Found: 326.0753. **EA**: Calcd. for $C_{15}H_{20}BrNO_2$: C 54.61, H 6.09, N 4.27. Found: C 55.23, H 6.18, N 4.29.

2-bromo-1-(1-piperidinyl)-1-propanone



A colourless oil was obtained from passing through neutral alumina using CH_2Cl_2 as an eluent, 90% yield. **^{1}H NMR** (499.797 MHz, $CDCl_3$, 27 °C): δ 1.75-1.55 (6H, m, 3 CH_2), 1.83 (3H, d, *J*=6.5 Hz, CH_3), 3.73-3.38 (4H, m, 2 CH_2), 4.60 (1H, q, *J*=6.5 Hz, CH), **^{13}C{^{1}H} NMR** (125.688 MHz, $CDCl_3$, 27 °C): δ 21.8 (CH_3), 24.4 (CH_2), 25.4 (CH_2), 26.1 (CH_2), 38.3 (CH), 43.5 (CH_2), 47.2 (CH_2), 167.3 (carbonyl). **HRMS (ESI)** m/z Calcd. for $C_8H_{14}BrNNaO$ $(M+Na)^+$: 242.0151.1254. Found: 242.0153. **EA**: Calcd. for $C_8H_{14}BrNO$: C 43.65, H 6.41, N 6.36. Found: C 43.78, H 6.48, N 6.39.

2-methoxy-1-(1-piperidinyl)-1-propanone

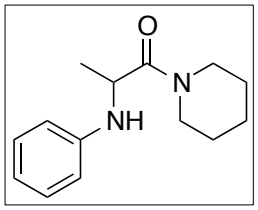


Sodium methoxide (0.96 g, 17.7 mmol, 1.3 equiv) was dissolved in 30 ml of distilled MeOH. A solution of 2-bromo-1-(1-piperidinyl)-1-propanone (3.0205 g, 13.6 mmol, 1 equiv) in 30 ml of distilled MeOH was transferred to the sodium methoxide-MeOH under the N_2 atmosphere. The resulting solution was refluxed for 2

hours and cooled down to room temperature. The reaction mixture was diluted and excess sodium methoxide was quenched by slow addition of water (40 ml), extracted with DCM (3 x 50 ml). The combined organic layer was washed with brine (50 ml) dried over sodium sulfate, and filtered. The organic solvent was then removed under reduced pressure to yield the crude product as a colorless oil (94.3 % crude yield). Purified by flash chromatography on a silica column with a 1:1 mixture of hexane:ethyl acetate as eluent (R_f=0.16). The isolated, purified yield of the colorless oil was 70%.

^{1}H NMR (499.797 MHz, $CDCl_3$, 27 °C): δ 1.38 (3H, d, *J*=6.5 Hz, CH_3), 1.67-1.56 (6H, m, 3 CH_2), 3.34 (3H, s), 3.59-3.55 (4H, m, 2 CH_2), 4.16 (1H, q, *J*=6.5 Hz, CH), **^{13}C{^{1}H} NMR** (125.688 MHz, $CDCl_3$, 27 °C): δ 17.6 (CH_3), 24.6 (CH_2), 25.8 (CH_2), 26.6 (CH_2), 43.3 (CH_2), 45.9 (CH_2), 76.8 (CH), 170.2 (carbonyl). **HRMS (ESI)** m/z Calcd. for $C_9H_{18}NO_2$ $(M+H)^+$: 172.1332 Found: 172.1333.

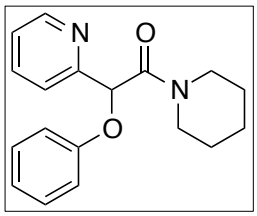
1-(*N*-phenyl-alanyl)-piperidine



2-bromo-1-(1-piperidinyl)-1-propanone (4 g, 18.2 mmol) and aniline (3.89 g, 36.4 mmol) were refluxed in benzene for 48 hours. After cooling to room temperature benzene was removed under reduced pressure and the resulting solid was dissolved in 60 mL of DCM. The organic layer was washed with 3x60 mL distilled H_2O, with 60 mL of brine, dried over sodium sulfate, and filtered. The organic solvent was then removed under reduced pressure to yield the crude product (95%, brownish solid). Purified by crystallization using CH_2Cl_2/Hexane, purified yield 50%, light brown solid.

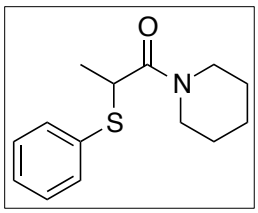
^{1}H NMR (499.797 MHz, $CDCl_3$, 27 °C): δ 1.38 (3H, d, *J*=6.5 Hz, CH_3), 1.54-1.71 (6H, m, 3 CH_2), 3.64-3.48 (4H, m, 2 CH_2), 4.43 (1H, q, *J*=6.5 Hz, CH), 4.7 (NH, br), 6.64-6.62 (2H, m, 2 aromatic CH), 6.73-6.69 (1H, m, 1 aromatic CH), 7.19-7.16 (2H, m, 2 aromatic CH). **^{13}C{^{1}H} NMR** (125.688 MHz, $CDCl_3$, 27.0 °C): δ 18.8 (CH_3), 24.5 (CH_2), 25.6 (CH_2), 26.5 (CH_2), 43.3 (CH_2), 46.4 (CH_2), 48.6 (CH), 113.5 (aromatic), 117.6 (aromatic), 129.3 (aromatic), 146.7 (aromatic), 171.7 (carbonyl). **HRMS (ESI)** m/z Calcd. for $C_{14}H_{21}N_2O$ $(M+H)^+$: 233.1648. Found: 233.1645. **EA**: Calcd. for $C_{14}H_{20}N_2O$: C 72.38, H 8.68, N 12.06. Found: C 72.39, H 8.77, N 12.02.

2-phenoxy-2-(2-pyridyl)-1-(1-piperidinyl)-ethanone



A solid substrate of 2-phenoxy-1-(piperidin-1-yl)ethanone (3.9275 g, 17.9 mmol) was weighed into a side arm flask, evacuate and refilled with Ar. The substrate was then dissolved in 15 ml of freshly distilled THF and cooled to -78 °C. A THF solution of Lithium bis(trimethylsillyl)amide (3.3 g, 19.7 mmol dissolved in 15 ml of freshly distilled THF), at to 0 °C, was cannulated to the side arm flask containing 2-phenoxy-1-(piperidin-1-yl)ethanone under Ar atmosphere over the course of 10 to 15 min. The resulting solution was stirred for another 30 min at -78 °C. 2-Chloropyridine (2.04 g, 1.7 mL, 17.9 mmol) was added using a gastight syringe and the resulting reaction mixture was allowed to warm to room temperature and stirred for 48 hours. After the reaction time, saturated NH_4Cl was added, and stirred for another 15 min. The reaction mixture was extracted with ethylacetate (4 x 50 ml) and the organic layers were combined, washed with brine (50 ml), dried over sodium sulfate, and filtered. The crude product (98% yield, off brown solid) was purified by flash chromatography on a silica column with a 3:2 mixture of hexane:ethyl acetate as eluent (R_f=0.12). The isolated, purified yield of the white solid was 45%.
^{1}H NMR (499.797 MHz, $CDCl_3$, 27.0 °C): δ 1.36-1.33 (1H, m, CH_2), 1.48-1.42 (2H, m, CH_2), 1.68-1.55 (3H, m, CH_2), 3.57-3.51 (2H, m, CH_2), 3.66-3.59 (2H, m, CH_2), 6.07 (1H, s, CH), 6.99-6.96 (1H, m, 1 aromatic CH), 7.04-7.02 (2H, m, 2 aromatic CH), 7.29-7.24 (3H, m, 3 aromatic CH), 7.75-7.66 (2H, m, 2 aromatic CH), 8.61-8.59 (1H, m, 1 aromatic CH). **^{13}C{^{1}H} NMR** (125.688 MHz, $CDCl_3$, 27.0 °C): δ 24.5 (CH_2), 25.5 (CH_2), 26.1 (CH_2), 43.6 (CH_2), 46.6 (CH_2), 79.8 (CH), 115.4 (aromatic), 121.7 (aromatic), 121.8 (aromatic), 123.2 (aromatic), 129.6 (aromatic), 137.0 (aromatic), 148.9 (aromatic), 156.7 (aromatic), 157.4 (aromatic), 166.5 (carbonyl). **HRMS (ESI)** m/z Calcd. for $C_{18}H_{20}N_2NaO_2$ $(M+Na)^+$: 319.1417. Found: 319.1421. **EA**: Calcd. for $C_{18}H_{20}N_2O_2$: C 72.95, H 6.80, N 9.45. Found: C 72.93, H 6.89, N 9.39.

2-phenylthio-1-(1-piperidinyl)-1-propanone



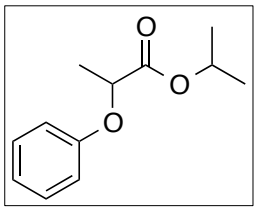
^{1}H NMR (499.118 MHz, $CDCl_3$, 27 °C): δ 1.49 (3H, d, *J*=7.0 Hz, CH_3), 1.79-1.52 (6H, m, 3 CH_2), 3.50-3.37 (3H, m, CH_2), 3.68-3.63 (1H, m, CH_2) 4.05 (1H, q, *J*=6.9 Hz, CH), 7.34-7.28 (3H, m, 3 aromatic CH), 7.48-7.46 (2H, m, 2 aromatic CH). **^{13}C{^{1}H} NMR** (125.691 MHz, $CDCl_3$, 27 °C): δ 18.5 (CH_3), 24.5 (CH_2), 25.6 (CH_2), 26.4 (CH_2), 42.6 (CH_2), 43.3 (CH_2), 47.1 (CH), 128.0 (aromatic), 128.8 (aromatic), 133.3 (aromatic), 133.5 (aromatic),

169.5 (carbonyl **HRMS (ESI)** m/z Calcd. for $C_{14}H_{20}NOS$ $(M+H)^+$: 250.1260. Found: 250.1261. **EA**: Calcd. for $C_{14}H_{19}NOS$: C 67.43, H 7.68, N 5.62. Found: C 67.59, H 7.66, N 5.59, S 12.74.

N, N-diphenyl-2-phenoxypropionamide (CAS #: 1021327-16-1)

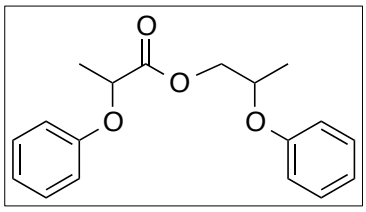
Prepared as previously reported.[7]

Synthesis of isopropyl 2-phenoxypropanoate



5 mL (5.9 g, 31.6 mmol) of 2-phenoxypropionyl chloride in 50 mL of DCM was cooled to 0 °C in an ice bath. 1.2 equiv (5.3 mL) of triethylamine was then added, followed by a drop wise addition of 3 equiv (7.2 mL) of isopropyl alcohol. The mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was washed with 4x25 mL of distilled H_2O and then washed with 30 mL of brine, dried over sodium sulfate, and filtered. The organic solvent was then removed under reduced pressure to yield the isopropyl ester (88%, yellow oil). **^{1}H NMR** (499.806 MHz, $CDCl_3$, 27.0 °C): δ 1.20 (3H, d, *J*=6.2 Hz, CH_3), 1.29 (3H, d, *J*=6.2 Hz, CH_3), 1.63 (3H, d, *J*=6.8 Hz), 4.73 (1H, q, *J*=6.7 Hz, CH), 5.10 (1H, septet, *J*=6.2 Hz, CH), 6.90 (2H, d, *J*=8.1 Hz, 2 aromatic CH), 6.99 (1H, t, *J*=7.3 Hz, 1 aromatic CH), 7.29 (2H, t, dd, *J*=8.4 Hz, 7.5 Hz, 2 aromatic CH). **^{13}C{^{1}H} NMR** (125.691 MHz, $CDCl_3$, 27.0 °C): δ 18.5 (CH_3), 21.6 (CH_3), 21.7 (CH_3), 68.8 (CH), 72.7 (CH), 115.1 (aromatic), 121.5 (aromatic), 129.5 (aromatic), 157.7 (aromatic), 171.9 (carbonyl). **HRMS (ESI)** m/z Calcd. for $C_{12}H_{16}NaO_3$ $(M+Na)^+$: 231.0993 Found: 231.0993.

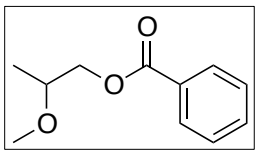
Synthesis of 2-phenoxypropyl 2-phenoxypropanoate.



The ester was prepared by reacting 2-phenoxypropionyl chloride (290 mg, 1.5 mmol) with racemic 2-phenoxypropan-1-ol (227.6 mg, 1.5 mmol) in DCM. The same procedure was followed as described above. Purified by flash chromatography on a silica column with a 9:1 mixture of hexane:ethyl acetate as eluent (R_f=0.23). The isolated, purified yield of the colorless oil was 70%. **^{1}H NMR** (399.984 MHz, $CDCl_3$, 27.0 °C): δ 1.28 (3H, d, *J*=6.7 Hz, CH_3), 1.59 (3H, t, *J*=6.5 Hz, CH_3), 4.21-4.26 (1H, m,

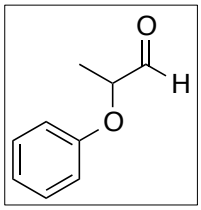
CH_2), 4.33-4.39 (1H, m, CH_2), 4.53-4.63 (1H, m, CH), 4.73-4.80 (1H, m, CH), 6.81-6.91 (4H, m, 4 aromatic CH), 6.92-6.99 (2H, m, 2 aromatic CH), 7.16-7.31 (4H, m, 4 aromatic CH). **$^{13}C\{^1H\}$ NMR** (125.691 MHz, $CDCl_3$, 27.0 °C): δ 16.6 (CH_3), 18.6 (CH_3), 67.4 (CH_2), 71.6 (CH), 72.4 (CH), 115.0 (aromatic), 115.1 (aromatic), 116.0 (aromatic), 116.1 (aromatic), 121.3 (aromatic), 121.6 (aromatic) 129.6 (aromatic), 157.5 (aromatic), 157.6 (aromatic), 172.1 (carbonyl). **HRMS (ESI)** m/z Calcd. for $C_{18}H_{20}NaO_4$ $(M+Na)^+$: 323.1254. Found: 323.1252.

2-methoxypropyl benzoate



The ester was prepared by reacting the hydrogenation product of 2-methoxy-1-(1-piperidinyl)-1-propanone (2-methoxypropanol, piperidine, isopropanol, unreacted starting material and THF) with excess benzoyl chloride (1.2 equiv with respect to 2-methoxypropanol, piperidine, and isopropanol in the reaction mixture) in CH_2Cl_2 using the same procedure described above. **^1H NMR** (499.118 MHz, $CDCl_3$, 27.0 °C): δ 1.29 (3H, d, *J*=6.5 Hz, CH_3), 3.46 (3H, s), 3.75-3.70 (1H, m, CH), 4.38-4.29 (2H, m, CH_2).

Synthesis of 2-phenoxypropanaldehyde.



The aldehyde was prepared by a modified version of a procedure previously reported.[8] 3.6 g (20 mmol) of methyl 2-phenoxypropanoate (prepared as described above) was dissolved in 50 mL of distilled anhydrous DCM under Ar and cooled to -78 °C. 25 mL of 1M diisobutylaluminum hydride was added dropwise by a cannula. The resulting mixture was stirred for 30 min at -78 °C. Reaction was quenched with 0.5 mL of methanol and the reaction mixture was allowed to warm to room temperature. The mixture was poured into 130 mL of DCM in a separatory funnel. The mixture was washed with 26 mL of 1M HCl, then 25 mL of brine, and then concentrated *in vacuo* to yield a colorless oil, crude yield >99%. The resulting clear oil was then purified by distillation at 50 °C under high vacuum.

^1H NMR (499.118 MHz, $CDCl_3$, 27.0 °C): δ 1.51 (3H, d, *J*=7.0 Hz, CH_3), 4.66 (1H, dq, *J*=1.8 Hz, 6.9 Hz, CH), 6.51 (2H, d, *J*=8.0 Hz, 2 aromatic CH), 7.03 (1H, t, *J*=7.4 Hz, aromatic CH), 7.32 (2H, dd, *J*=7.7 Hz, 8.3 Hz, 2 aromatic CH), 9.75 (1H, d, *J*=1.8 Hz, aldehyde). **$^{13}C\{^1H\}$ NMR** (125.691 MHz, $CDCl_3$, 27.0 °C): δ 15.6 (CH_3), 77.8 (CH), 115.3 (aromatic), 121.9 (aromatic), 129.8 (aromatic), 157.3 (aromatic), 202.5 (carbonyl). **HRMS (EI)** m/z: Calcd. for $C_9H_{10}O_2$ (M^+, 27.29%) 150.0680; Found 150.0681. 121.0655 (100%), 97.1019 (22.13%), 93.0701 (29.61%), 69.0700 (18.62%).

Synthesis of ruthenium precursor.

trans-$RuCl_2$((*S*,*S*)-skewphos)((*R*,*R*)-dpen) (**14**) was prepared as reported previously.[9]

General procedure for the synthesis of racemic alcohol products from the parent amides

The racemic alcohols were prepared by a modified version of our previously reported hydrogenation procedure.[10] The achiral amide hydrogenation catalyst, [Ru(η^3-C_3H_5)($Ph_2PCH_2CH_2NH_2$)$_2$]BF_4 (6.8 mg, 0.010 mmol), and KO^{t}Bu (11.2 mg, 0.1 mmol) were weighed out into two separate NMR tubes inside the glove box. Freshly distilled THF (1.0 mL) was then added to the NMR tube containing the ruthenium-allyl precursor by using a cannula under Ar pressure. The Ar was purged with H_2 gas. Under H_2, the solution of the ruthenium precursor was transferred by cannula into the tube containing the KO^{t}Bu. The tube was then pressurized to ~ 2 psi gauge pressure. The resulting reddish-yellow solution was then transferred with a cannula under H_2 to the autoclave containing the amide substrate (0.5 mmol, 50 equiv). A THF solution (4.0 mL) was used to rinse the NMR tube containing the catalyst into the autoclave. The autoclave containing the amide was purged with H_2 gas for 15-20 min prior to transfer of the Ru catalyst. The autoclave was then pressurized to 50 atm H_2 and stirred at 80 °C overnight. After 24 h, the reaction mixture was allowed to cool to room temperature, the autoclave was then slowly depressurized and opened to the atmosphere. The catalyst was removed by passing the solution through a florisil plug using CH_2Cl_2 as the rinse solvent. The solvent was then removed under reduced pressure using a rotary evaporator. The ^{1}H NMR spectra ($CDCl_3$) were identical to those of the 2-aryloxy propanols obtained from the asymmetric hydrogenations. The NMR yields of all these racemic hydrogenations with [Ru(η^3-C_3H_5)($Ph_2PCH_2CH_2NH_2$)$_2$]BF_4 were 100 %. The racemic products were also analyzed by GC-MS or HPLC (Figure S44).

Synthesis of sodium isopropoxide.

0.1–0.2 g (4.35–8.7 mmol) of freshly cut sodium metal was placed into a side arm flask and purged with N_2 gas. Freshly distilled anhydrous isopropyl alcohol (20 mL) was then transferred to the flask containing the sodium, using a cannula under N_2. The solution was stirred at room temperature overnight. The resulting solution was decanted into another side arm flask and

concentrated under reduced pressure using a schlenk line to yield a white powder. This powder was then dried under high vacuum overnight. The remaining sodium particles were deactivated by careful addition of isopropyl alcohol, ethanol, and water respectively under the N_2 atmosphere.

Note: the color of the sodium isopropoxide changed from white to pale pink over a period of time inside the glove box, so freshly prepared sodium isopropoxide was used for every hydrogenation reaction.

General procedure for lab-scale enantioselective hydrogenations (Table 2).

trans-$RuCl_2$((*S*,*S*)-skewphos)(*R*,*R*)-dpen) (**14**) (24.5 mg, 30 μmol) and the base, 2-PrONa (123.0 mg, 1500 μmol, 2.5 equiv to substrate) were weighed into 2 separate NMR tubes inside a glove box. Freshly distilled THF (1.0 mL each) was cannulated into the NMR tubes containing **14** and the base under Ar pressure. 2-PrOH (1200 μmol, 90 μL, 2.5 equiv to substrate) was also added to the NMR tube containing the base using a gas-tight syringe.

Solid amides: An amide (600 μmol, 20 equiv) was added to a stainless steel autoclave equipped with a stir bar. The autoclave was then assembled and purged with H_2 (1 atm) for 15-20 min. A THF solution of the catalyst precursor (prepared above) was transferred into the autoclave under H_2 pressure using a cannula. This was followed by the 2-PrONa /2-PrOH/THF. Freshly distilled THF (3.0 mL) was then used to rinse the NMR tubes to ensure quantitative transfers. The autoclave was then sealed and pressurized to 4 atm H_2. The reaction mixture was stirred at room temperature for 24 hours. The reaction was stopped by depressurizing the autoclave and opening it to air. The catalyst was removed by passing the solution through a florisil plug using CH_2Cl_2 as the rinse solvent. The solvent was then removed under reduced pressure using a rotary evaporator. (See Figures S23-S43 for NMR spectra and Figures S44 for GC-MS or HPLC chromatograms of the products).

Liquid amides: The autoclave was fitted with a magnetic stir bar and then purged with H_2 for 10 min. The pre-weighed amide (600 μmol, 20 equiv) was dissolved in freshly distilled THF (1.0 mL) under Ar. The amide was then transferred into the autoclave using a cannula. The autoclave was then purged with H_2 for another 10 min. The THF solution of the catalyst precursor (prepared

above) was then transferred into the autoclave under H_2 pressure using a cannula. This was then followed by the 2-PrONa/2-PrOH/THF solutions. Freshly distilled THF (2 mL) was then used to rinse the NMR tubes to ensure the quantitative transfers. The autoclave was then sealed and pressurized to 4 atm H_2. The reaction mixture was stirred at room temperature for 24 hours. The reaction was stopped by depressurizing the autoclave and opening it to air. The catalyst was removed by passing the solution through a florisil plug using CH_2Cl_2 as the rinse solvent. The solvent was then removed under reduced pressure using a rotary evaporator. The NMR spectra, GC-MS, or HPLC chromatograms of the products are shown below.

High turnover number enantioselective hydrogenation of 17

The procedure for liquid amide was followed with 4.95 mg (6 μmol) of *trans*-$RuCl_2$((*S*,*S*)-skewphos)(*R*,*R*)-dpen) (**14**), 123.0 mg of 2-PrONa (1500 μmol, 2.5 equiv to substrate), 50 μL of 2-PrOH (600 μmol, 1 equiv to substrate) and 150.78 mg of **17** (600 μmol, 100 equiv to catalyst). The hydrogenation was performed at 50 atm H_2 pressure and room temperature for 24 hours. The pressure was released and the reactor opened to air. The reaction mixture was then passed through the florisil plug using CH_2Cl_2 as the rinse solvent. The solvent was then removed under reduced pressure using a rotary evaporator to give the crude product (99.5 mg, 97.4%) as the colorless oil. The NMR spectrum and GC-MS chromatogram were qualitatively identical those of the small-scale hydrogenation.

***Purification of reaction product, 2-(3-fluorophenoxy)propan-1-ol by column chromatography* (Table 2, entry 7)**

The reaction was repeated with 34.5 mg (41.8 μmol) of *trans*-$RuCl_2$((*S*,*S*)-skewphos)(*R*,*R*)-dpen) (**14**), 173.0 mg of 2-PrONa (2109.5 μmol, 2.5 equiv to substrate), 125 μL of 2-PrOH (1673 μmol, 2 equiv to substrate) and 210.5 mg of 2-(3-fluorophenoxy)propan-1-ol (836.6 μmol, 20 equiv to catalyst). The hydrogenation was performed at 4 atm H_2 pressure and room temperature for 24 hours. The pressure was released and the reactor was opened to air. The reaction mixture was then passed through a florisil plug using CH_2Cl_2 (75 mL) as the rinse solvent. The solvent was then removed under reduced pressure using a rotary evaporator to give the crude product (145 mg, >100%) as a reddish oil. The ^{1}H NMR spectrum was recorded (in $CDCl_3$) by taking an aliquot from the reaction mixture. The ^{1}H NMR spectrum supported 100% conversion of the starting material. The crude product was purified, to yield a colorless oil, using flash chromatography on a silica column with a 4:1 mixture of hexane:ethyl acetate eluent (Rf=0.19).

The purified yield of the colorless oil was 121 mg (~95%). The product turned to bluish purple color over time (in a day). However the NMR showed no decomposition. **EA**: Calcd. for $C_9H_{11}FO_2$: C 63.52, H 6.52. Found: C 63.61, H 6.55. (For ^{1}H NMR refer the Figure S31).

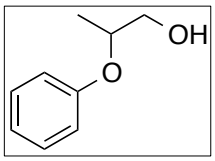
Spectroscopic identification of alcohol products

The following methods were used to determine the %ee of the product alcohols:

Method A: GC analysis using Supelco Beta DEX 225 capillary column (30 m × 0.25 mm × 0.25 μm film thickness, He 1 mL/min, temperature programmed from 100 °C to 220 °C at 5 °C/min).

Method B: HPLC analysis using Daicel CHIRALPAK IB (4.6 mm i.d. x 250 mm) chiral column, Hex:2-PrOH = 97:3, 0.8 mL/min, at 30 °C.

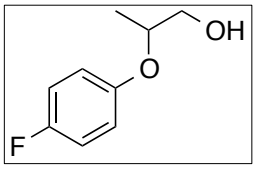
2-phenoxypropan-1-ol (entry 1)[11]



Colorless oil, 87% yield, 97% *ee*. $[\alpha]_D^{22}$ = -29.3 (c=1.87, g/100 mL, $CHCl_3$). **^{1}H NMR** (498.118 MHz, $CDCl_3$, 27 °C): δ 1.29 (3H, d, J = 6.0 Hz, CH_3), 2.12 (1H, brs, OH), 3.70-3.81 (2H, m, CH_2), 4.50-4.54 (1H, m, CH), 6.94-7.01 (3H, m, aromatic CH), 7.28-7.37 (2H, m, aromatic CH); **^{13}C{^{1}H} NMR** (125.691 MHz, $CDCl_3$, 27 °C): δ 15.8 (CH_3), 66.4 (CH_2), 74.7 (CH), 116.2 (aromatic), 121.3 (aromatic), 129.6 (aromatic), 157.7 (aromatic). **HRMS (EI)**: m/z 94.0425 (100%), 152.0838 (M^+) (21.89%), 77.0392 (13.96%), 121.0652 (13.22%)

%*ee* was determined using method A, Retention times: t_R (minor) = 11.24 min, t_R (major) = 11.45 min.

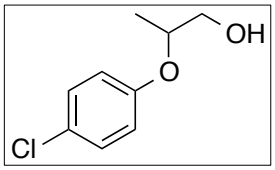
2-(4-fluorophenoxy)propan-1-ol (entry 2)[12]



Colorless oil, 87% yield, 96% *ee*. $[\alpha]_D^{22}$ = -25.7 (c=0.86, g/100 mL, $CHCl_3$). **^{1}H NMR** (498.118 MHz, $CDCl_3$, 27 °C): δ 1.27 (3H, d, *J* = 6.4 Hz, CH_3), 2.14 (1H, brs, OH), 3.69-3.80 (2H, m, CH_2), 4.38-4.44 (1H, m, CH), 6.88-6.93 (2H, m, aromatic CH), 6.98-7.01 (2H, m, aromatic CH); **^{13}C{^{1}H} NMR** (125.691 MHz, $CDCl_3$, 27 °C): δ 15.8 (CH_3), 66.3 (CH_2), 75.9 (CH), 115.9 (d, *J* = 23.1 Hz, aromatic), 117.6 (aromatic), 153.7 (aromatic), 157.9 (d, *J* = 239.2 Hz, aromatic). **HRMS (EI)**: m/z 112.0320 (100%), 94.0419 (21.66%), 57.0704 (20.65%), 170.0740 (M^+) (11.57%)

%*ee* was determined using method A, Retention times: t_R (minor) = 11.95 min, t_R (major) = 12.12 min.

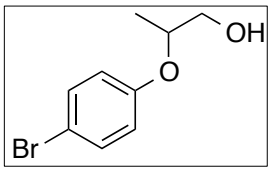
2-(4-chlorophenoxy)propan-1-ol (entry 3)[11]



Colorless oil, 91.7% yield, >99% *ee*. $[\alpha]_D^{22}$ = -33.1 (c=1.11, g/100 mL, $CHCl_3$). **^{1}H NMR** (498.118 MHz, $CDCl_3$, 27 °C): δ 1.28 (3H, d, *J* = 6.4 Hz, CH_3), 2.01 (1H, brs, OH), 3.69-3.80 (2H, m, CH_2), 4.43-4.50 (1H, m, CH), 6.86-6.90 (2H, m, aromatic CH), 7.23-7.27 (2H, m, aromatic CH); **^{13}C{^{1}H} NMR** (125.691 MHz, $CDCl_3$, 27 °C): δ 15.7 (CH_3), 66.2 (CH_2), 75.3 (CH), 117.5 (aromatic), 126.1 (aromatic), 129.5 (aromatic), 156.3 (aromatic). **HRMS (EI)**: m/z 128.0027 (23.53%), 186.04481 (M^+) (3.33%)

%*ee* was determined using method A, Retention times: t_R (minor) = 17.05 min, t_R (major) = 17.19 min.

2-(4-bromophenoxy)propan-1-ol (entry 4)[13]

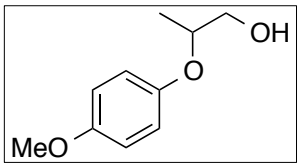


Colorless oil, 94% yield, >99% *ee*. $[\alpha]_D^{22}$ = -27.3 (c=1.88, g/100 mL, $CHCl_3$). **^{1}H NMR** (498.118 MHz, $CDCl_3$, 27 °C): δ 1.28 (3H, d, *J* = 7.4 Hz, CH_3), 2.05 (1H, brs, OH), 3.69-3.80 (2H, m, CH_2), 4.43-4.50 (1H, m, CH), 6.83 (2H, d, *J* = 6.4 Hz, aromatic CH), 7.40 (2H, d, *J* = 6.4 Hz, aromatic CH); **^{13}C NMR** (125.691 MHz, $CDCl_3$, 27 °C): δ 15.7 (CH_3), 66.2 (CH_2), 75.2 (CH),

113.4 (aromatic), 117.9 (aromatic), 132.4 (aromatic), 156.8 (aromatic). **HRMS (EI)**: m/z 171.9531 (100%), 94.0420 (58.57%), 65.0394 (36.32%), 229.9944 (M^+) (26.49%).

%*ee* was determined using method A, Retention times: t_R (minor) = 19.38 min, t_R (major) = 19.49 min.

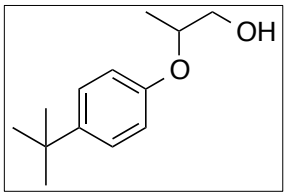
2-(4-methoxyphenoxy)propan-1-ol (entry 5)[14]



Colorless oil, 78.1% yield, 97% *ee*. $[\alpha]_D^{22}$ = -15.0 (c=1.32, g/100 mL, $CHCl_3$). **^{1}H NMR** (498.118 MHz, $CDCl_3$, 27 °C): δ 1.25 (3H, d, *J* = 6.4 Hz, CH_3), 2.17 (1H, brs, OH), 3.68-3.78 (2H, m, CH_2), 3.78 (3H, s, CH_3), 4.36-4.40 (1H, m, CH), 6.83-6.86 (2H, m, aromatic CH), 6.88-6.91 (2H, m, aromatic CH); **^{13}C NMR** (125.691 MHz, $CDCl_3$, 27 °C): δ 15.9 (CH_3), 55.7 (CH_3), 66.4 (CH_2), 76.1 (CH), 114.7 (aromatic), 117.8 (aromatic), 151.6 (aromatic), 154.6 (aromatic). **HRMS (EI)**: m/z 124.0522 (100%), 109.02881 (50.06%), 182.0940 (M^+) (23.17%)

%*ee* was determined using method A, Retention times: t_R (minor) = 17.25 min, t_R (major) = 17.36 min.

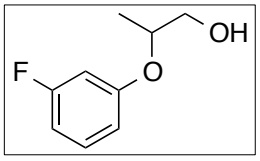
2-(4-tert-butylphenoxy)propan-1-ol (entry 6)



Colorless oil, 84% yield, 97% *ee*. $[\alpha]_D^{22}$ = -28.7 (c=1.01, g/100 mL, $CHCl_3$). **^{1}H NMR** (498.118 MHz, $CDCl_3$, 27 °C): δ 1.29 (3H, d, *J* = 6.5 Hz, CH_3), 1.32 (9H, s, CH_3), 2.08 (1H, brs, OH), 3.70-3.80 (2H, m, CH_2), 4.45-4.55 (1H, m, CH), 6.89 (2H, d, *J* = 8.9 Hz, aromatic CH), 7.32 (2H, d, *J* = 8.9 Hz, aromatic CH): **^{13}C NMR** (125.691 MHz, $CDCl_3$, 27 °C): δ 15.9 (CH_3), 31.5 (CH_3), 66.4 (CH_2), 74.8 (CH), 115.6 (aromatic), 126.4 (aromatic), 143.9 (aromatic), 155.4 (aromatic). **HRMS (ESI)** Calcd. for $C_{13}H_{20}O_2Na$ $(M+Na)^+$: 231.1356. Found : 231.1353

%*ee* was determined using method A, Retention times: t_R (minor) = 17.97 min, t_R (major) = 18.07 min.

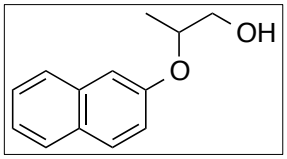
2-(3-fluorophenoxy)propan-1-ol (entry 7)



Colorless oil, 99% yield, 96% *ee*. $[\alpha]_D^{22}$ = -42.5 (c=1.66, g/100 mL, $CHCl_3$). **^{1}H NMR** (498.118 MHz, $CDCl_3$, 27 °C): δ 1.30 (3H, d, *J* = 6.3 Hz, CH_3), 1.99 (1H, brs, OH), 3.69-3.80 (2H, m, CH_2), 4.46-4.53 (1H, m, CH), 6.64-6.71 (2H, m, 2 aromatic CH), 6.72-6.75 (1H, m, aromatic CH), 7.21-7.27 (1H, m, aromatic CH). **^{13}C NMR** (125.691 MHz, $CDCl_3$, 27 °C): δ = 15.8 (CH_3), 66.3 (CH_2), 75.9 (CH), 115.9 (d, *J* = 23.1 Hz, aromatic), 117.6 (aromatic), 153.7 (aromatic), 157.9 (d, *J* = 239.2 Hz, aromatic). **HRMS (EI)**: m/z 112.0325 (100%), 170.0740 (M^+) (34.84%), 139.0560 (17.08%), 95.0300 (12.48%)

%*ee* was determined using method A, Retention times: t_R (minor) = 11.88 min, t_R (major) = 12.04 min.

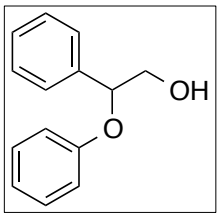
2-(naphthalene-2-yloxy)propan-1-ol (entry 8)[15]



Colorless oil, 93.5% yield, 90% *ee*. $[\alpha]_D^{22}$ = -34.3 (c=2.92, g/100 mL, $CHCl_3$). **^{1}H NMR** (498.118 MHz, $CDCl_3$, 27 °C): δ 1.37 (3H, d, *J* = 6.5 Hz, CH_3), 2.06 (1H, brs, OH), 3.77-3.87 (2H, m, CH_2), 4.65-4.72 (1H, m, CH), 7.17-7.20 (1H, m, aromatic CH), 7.23-7.25 (1H, m, aromatic CH), 7.34-7.38 (1H, m, aromatic CH), 7.44-7.49 (1H, m, aromatic CH), 7.72-7.75 (1H, m, aromatic CH), 7.77-7.81 (2H, m, aromatic CH): **^{13}C NMR** (125.691 MHz, $CDCl_3$, 27 °C): δ = 15.8 (CH_3), 66.3 (CH_2), 74.7 (CH), 109.0 (aromatic), 119.5 (aromatic), 123.8 (aromatic), 126.4 (aromatic), (126.7 (aromatic), 127.6 (aromatic), 129.2 (aromatic), 129.6 (aromatic), 134.5 (aromatic), 155.5(aromatic). **HRMS (EI)**: m/z 144.0576 (100%), 94.0420 (27.28%), 202.0990 (M^+) (21.90%)

%*ee* was determined using method A with the temperature gradient of 2 °C/min, Retention times:. t_R (major) = 48.14 min, t_R (minor) = 47.85 min.

2-Phenoxy-2-phenylethyl alcohol (entry 9)[16]

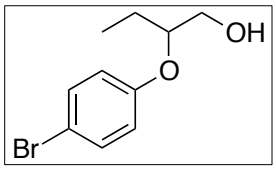


White solid, 91.7% yield, 84% *ee*. $[\alpha]_D^{22}$ = -19.1 (c=3.05, g/100 mL, $CHCl_3$). **^{1}H NMR** (498.118 MHz, $CDCl_3$, 27 °C): δ 2.26 (1H, brs, OH), 3.80-3.88

(1H, m, CH_2), 3.92-3.98 (1H, m, CH_2), 5.27-5.31 (1H, m, CH), 6.88-6.95 (3H, m, aromatic CH), 7.19-7.24 (2H, m, 2 aromatic CH), 7.29-7.33 (1H, m, aromatic CH), 7.35-7.41 (4H, m, 4 aromatic CH); **^{13}C NMR** (125.691 MHz, $CDCl_3$, 27 °C): δ = 67.6 (CH_2), 81.1 (CH), 115.9 (aromatic), 121.2 (aromatic), 126.3 (aromatic), 128.2 (aromatic), 128.7 (aromatic), 129.4 (aromatic), 137.8 (aromatic), 157.8 (aromatic). **HRMS (EI)**: m/z 94.0418 (100%), 120.0574 (34.00%), 91.0546 (32.69%), 214.0992 (M^+) (3.02%)

%*ee* was determined using method B, Retention times:. t_R (major) = 20.68 min, t_R (minor) = 27.45 min.

2-(4-bromophenoxy)butan-1-ol (entry 10)



Colorless oil, 60% yield, 95% *ee*. $[\alpha]_D^{22}$ = +3.46 (c=2.42, g/100 mL, $CHCl_3$). **^{1}H NMR** (498.118 MHz, $CDCl_3$, 27 °C): δ 0.96 (3H, t, *J* = 7.5 Hz, CH_3), 1.64-1.77 (2H, m, CH_2), 1.80-1.90 (1H, brs, OH), 3.75-3.85 (2H, m, CH_2), 4.25-4.30 (1H, m, CH) 6.80-6.87 (2H, m, aromatic CH), 7.38-7.41 (2H, m, aromatic CH); **HRMS (EI)**: m/z 171.9525 (100%), 94.0420 (37.86%), 65.0392 (14.17%), 244.0096 (M^+) (14.26%).

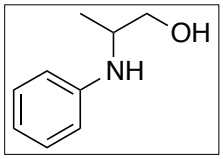
%*ee* was determined using method A, Retention times: t_R (minor) = 20.64 min, t_R (major) = 20.75 min.

2-methoxypropanol (entry 11)

The conversion was calculated using NMR recorded from the aliquot of the reaction mixture (See Figure S35 for more details). The %*ee* was obtained from the benzoyl chloride derivative.

%*ee* was determined using method A with the temperature gradient of 3 °C/min, Retention times: t_R (major) = 20.32 min, t_R (minor) = 20.39 min.

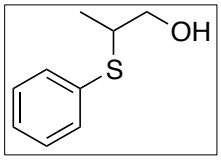
2-anilino-1-propanol (entry 12)[17]



47.5% yield, 74% *ee*. **^{1}H NMR** (498.118 MHz, $CDCl_3$, 27.0 °C): δ 1.22 (3H, d, *J*=6.5 Hz, CH_3), 3.56-3.49 (1H, m, CH), 3.70-3.65 (1H, m, CH), 3.77-3.73 (1H, m, CH), 6.80-6.70 (3H, m, aromatic CH), 7.23-7.18 (2H, m, aromatic CH);

%*ee* was determined using method B, Retention times: t_R (major) = 46.52 min, t_R (minor) = 35.84 min.

2-(phenylthio)-1-propanol (entry 14)



16% yield, 74% *ee*. **^{1}H NMR** (498.118 MHz, $CDCl_3$, 27.0 °C): δ 1.33 (3H, d, *J*=7 Hz, CH_3), 3.36-3.30 (1H, m, CH), 3.66-3.44 (2H, m, CH), 7.33-7.28 (3H, m, aromatic CH), 7.49-7.45 (2H, m, aromatic CH);

%*ee* was determined using method A with the temperature gradient of 2 °C/min, Retention times: t_R (major) = 25.86 min, t_R (minor) = 25.45 min.

^{1}H NMR spectra for the hydrogenation of racemic amides using 5 mol% of **14**, 250 mol% 2-PrONa, and 200 mol% 2-PrOH under 4 atm H_2 at RT in 24 h. (Refer to Table 2 of the manuscript for percent conversions).

Alcohol Product denoted by (∗)
Starting Material denoted by (♦)
Residual Solvent denoted by (δ)
Side Product denoted by (x)

Figure S23. The δ region from 8 to 1 ppm showing the comparison of the major alcohol product obtained from the hydrogenation of 2-phenoxy-1-(1-piperidinyl)-1-propanone with the starting material.

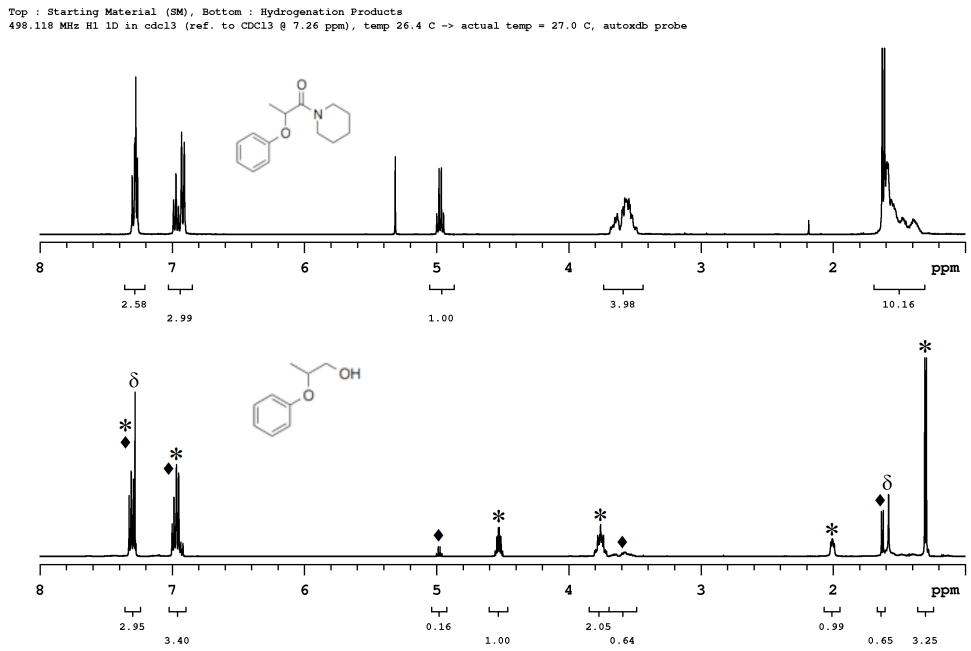


Figure S24. The δ region from 8 to 1 ppm showing the comparison of the major alcohol product obtained from the hydrogenation of 2-phenoxy-1-(1-piperidinyl)-1-propanone with the starting material. (The hydrogenation performed with 1.1 equiv of KO^{t}Bu; Table 1, entry 9)

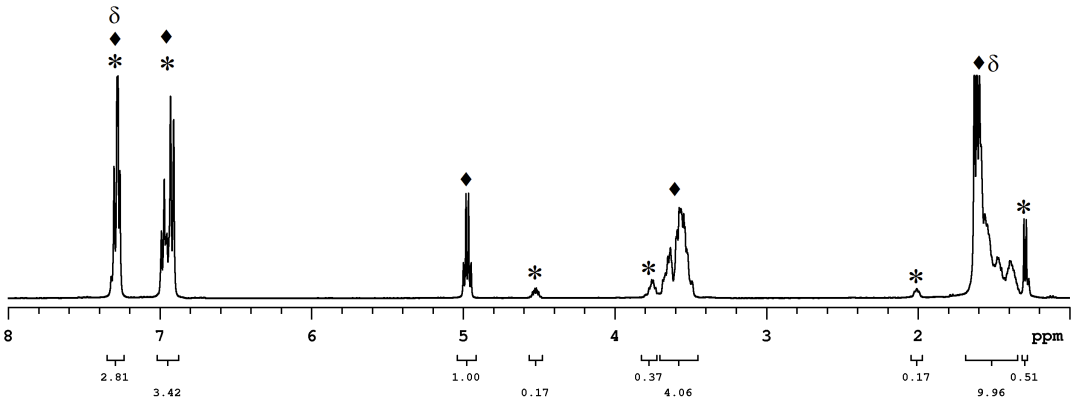


Figure S25. The δ region from 8 to 1 ppm, showing the comparison of the major alcohol product obtained from the hydrogenation of 2-(4-fluorophenoxy)-1-(1-piperidinyl)-1-propanone with the starting material.

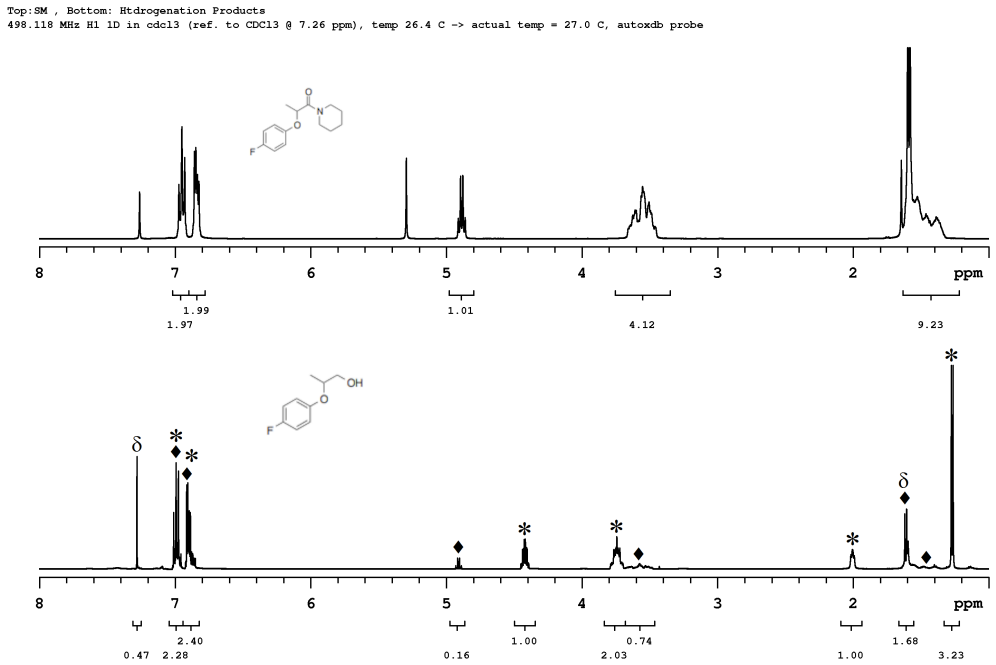


Figure S26. The δ region from 8 to 1 ppm, showing the comparison of the major alcohol product obtained from the hydrogenation of 2-(4-chlorophenoxy)-1-(1-piperidinyl)-1-propanone with the starting material.

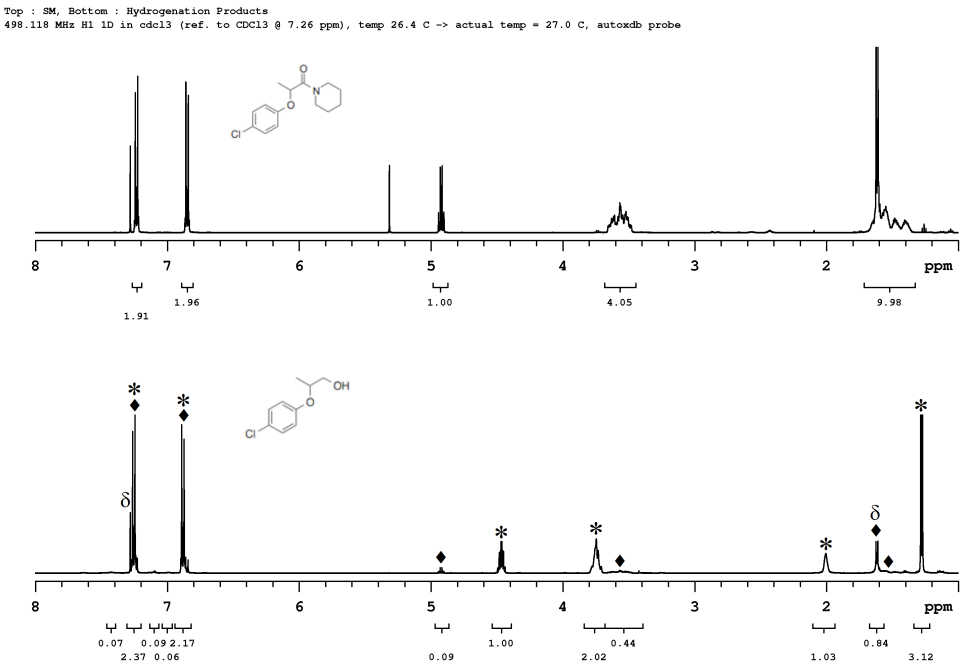


Figure S27. The δ region from 8 to 1 ppm, showing the comparison of the major alcohol product obtained from the hydrogenation of 2-(4-bromophenoxy)-1-(1-piperidinyl)-1-propanone with the starting material.

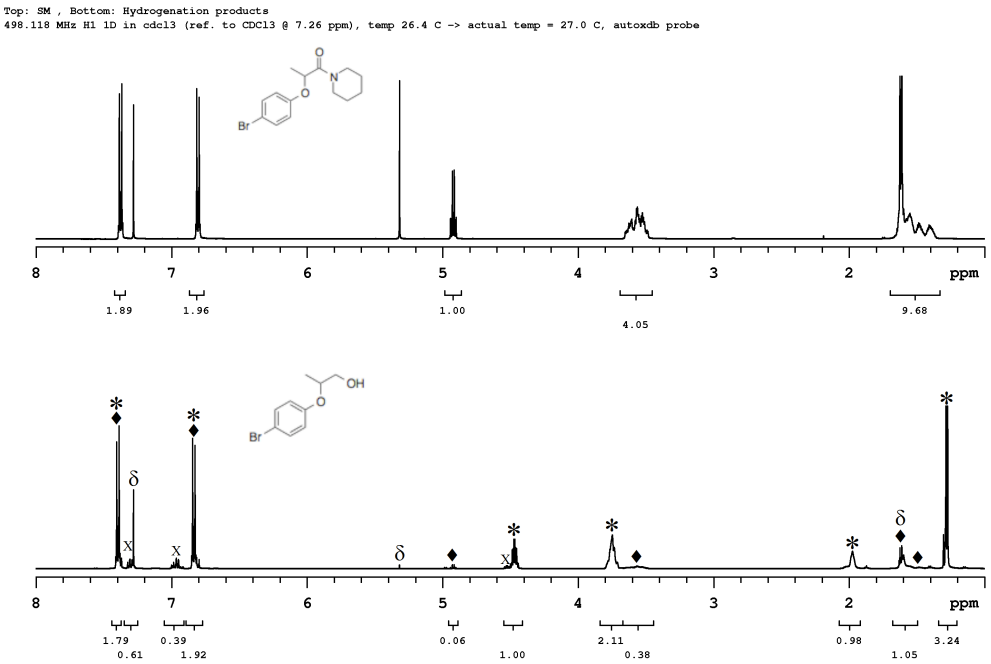


Figure S28. The δ region from 8 to 1 ppm showing the comparison of the major alcohol product obtained from the hydrogenation of 2-(4-methoxyphenoxy)-1-(1-piperidinyl)-1-propanone with the starting material.

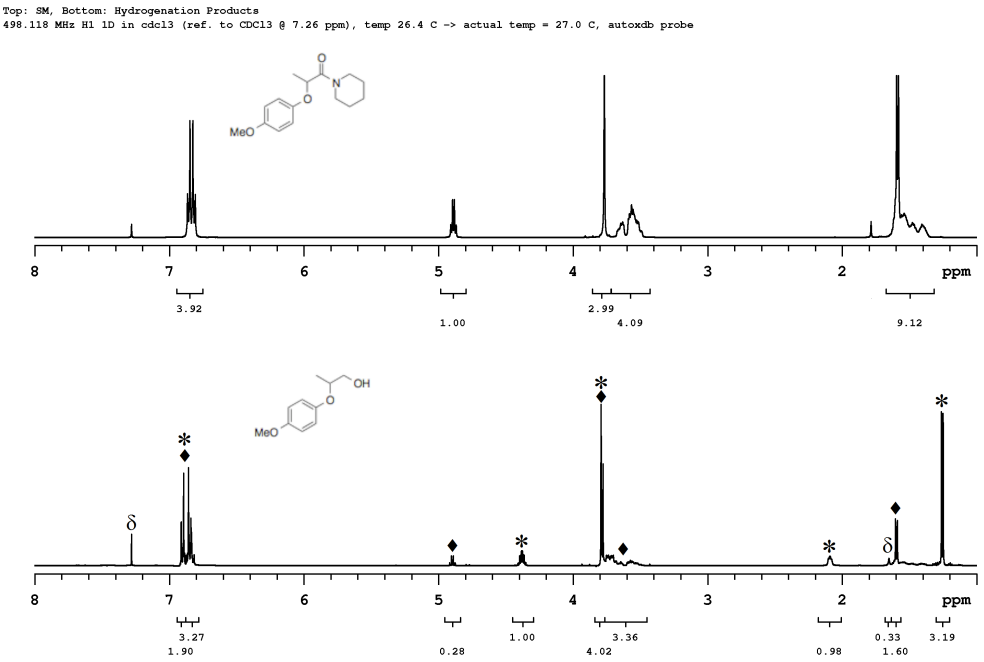


Figure S29. The δ region from 8 to 1 ppm showing the comparison of the major alcohol product obtained from the hydrogenation of 2-[4-(1,1-dimethylethyl)phenoxy]-1-(1-piperidinyl)-1-propanone with the starting material.

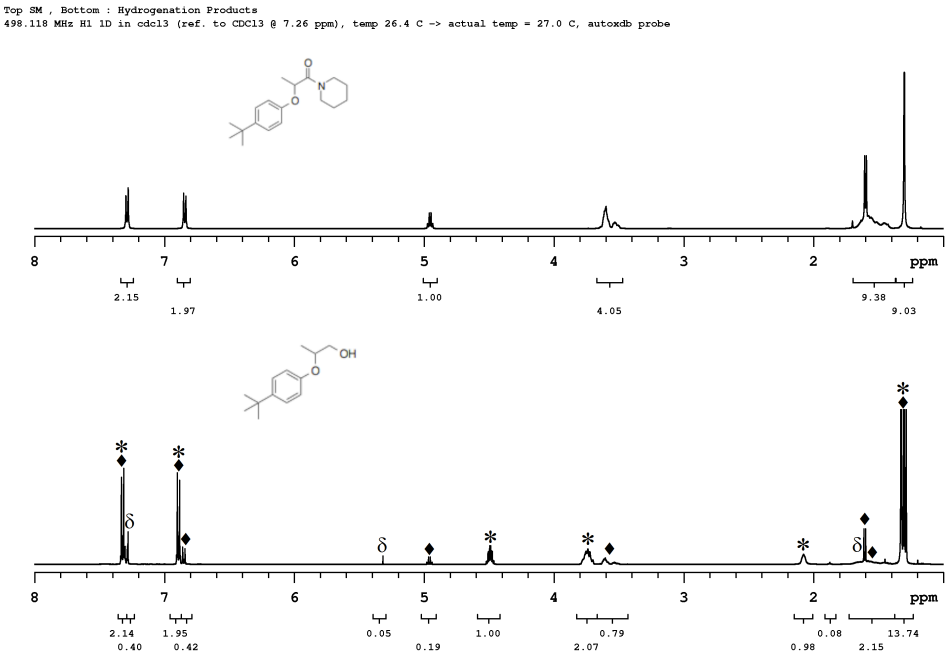


Figure S30. The δ region from 8 to 1 ppm showing the comparison of the major alcohol product obtained from the hydrogenation of 2-(3-fluorophenoxy)-1-(1-piperidinyl)-1-propanone with the starting material.

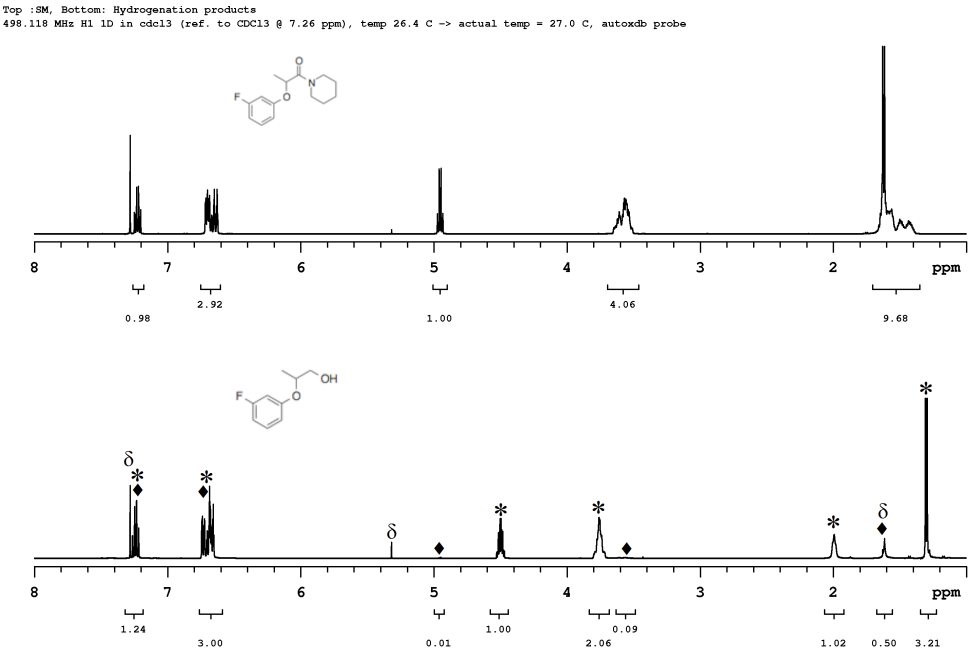


Figure S31. The δ region from 8 to 1 ppm showing the alcohol product (column purified) obtained from the hydrogenation of 2-(3-fluorophenoxy)-1-(1-piperidinyl)-1-propanone.

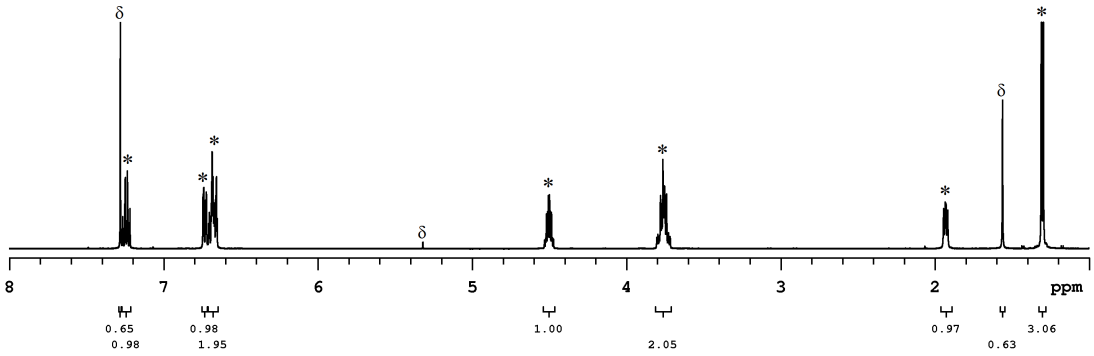


Figure S32. The δ region from 8 to 1 ppm, showing the comparison of the major alcohol product obtained from the hydrogenation of 2-(2-naphthalenyloxy)-1-(1-piperidinyl)-1-propanone with the starting material.

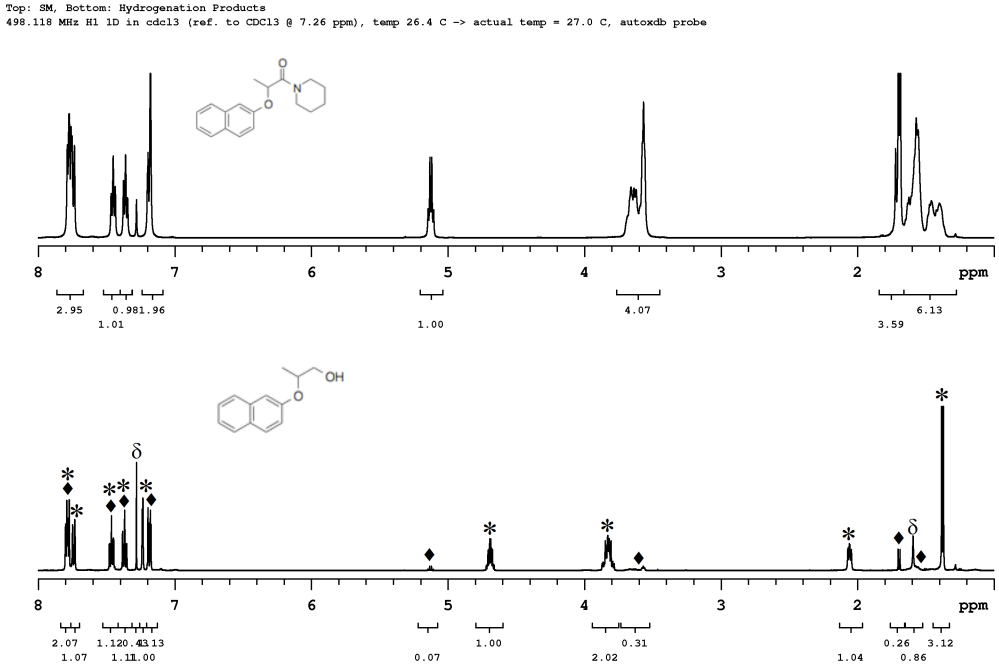


Figure S33. The δ region from 8 to 1 ppm, showing the comparison of the major alcohol product obtained from the hydrogenation of 2-phenoxy-2-phenyl-1-(1-piperidinyl)-ethanone with the starting material.

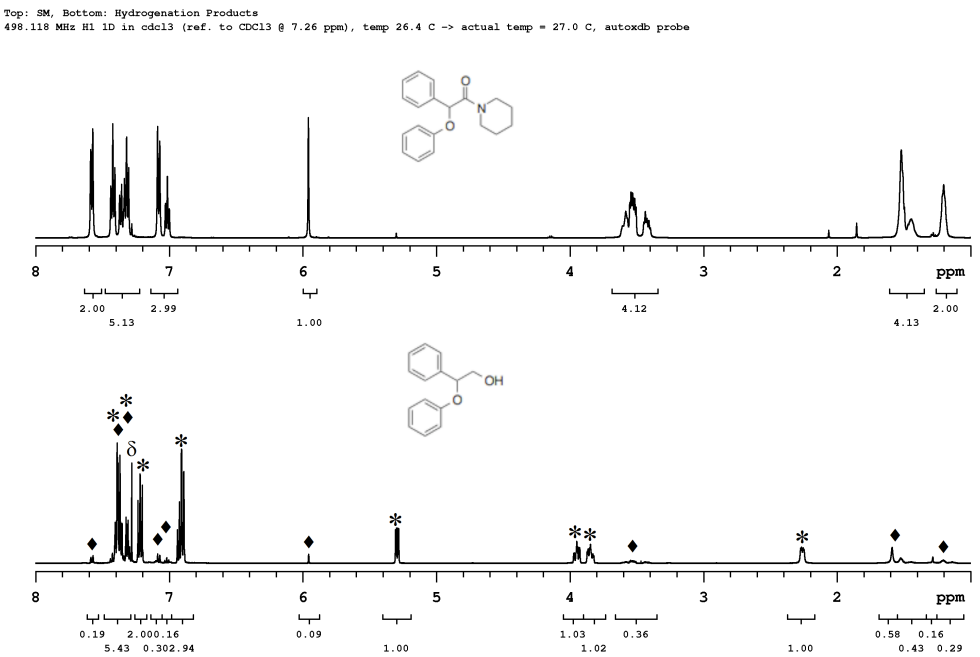


Figure S34. The δ region from 8 to 1 ppm, showing the comparison of the major alcohol product obtained from the hydrogenation of 2-(4-bromophenoxy)-1-(1-piperidinyl)-1-butanone with the starting material.

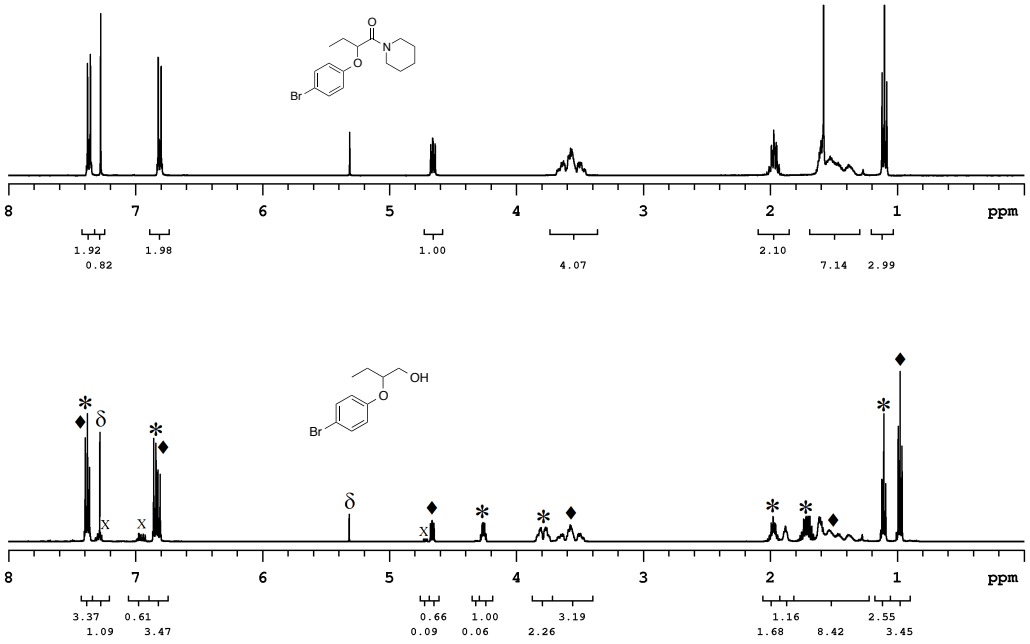


Figure S35. The δ region from 5 to 1 ppm showing the major alcohol product obtained from the hydrogenation of 2-methoxy-1-(1-piperidinyl)-1-propanone with the starting material (Due to low

boiling point of the major alcohol product NMR recorded using the aliquot taken directly from the reaction mixture, ρ = piperidine).

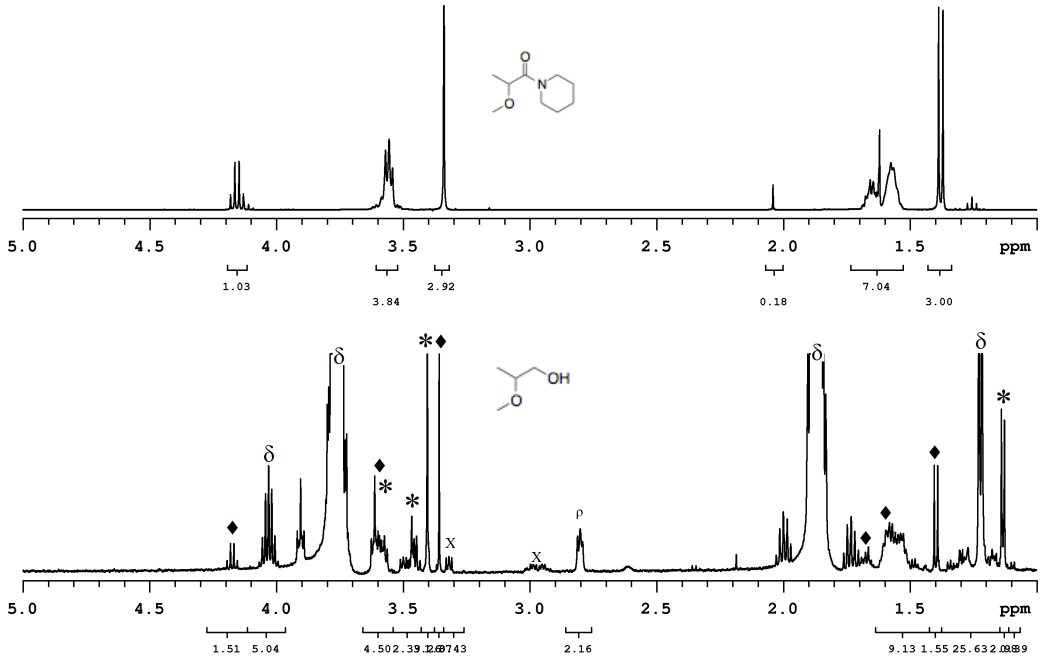


Figure S36. The δ region from 8 to 1 ppm showing the major alcohol product obtained from the hydrogenation of 1-(*N*-phenyl-alanyl)-piperidine with the starting material.
(Top: starting material, Middle : Hydrogenation product obtained under the normal conditions, Bottom: Hydrogenation product obtained at 0 °C under 50 atm hydrogen pressure)

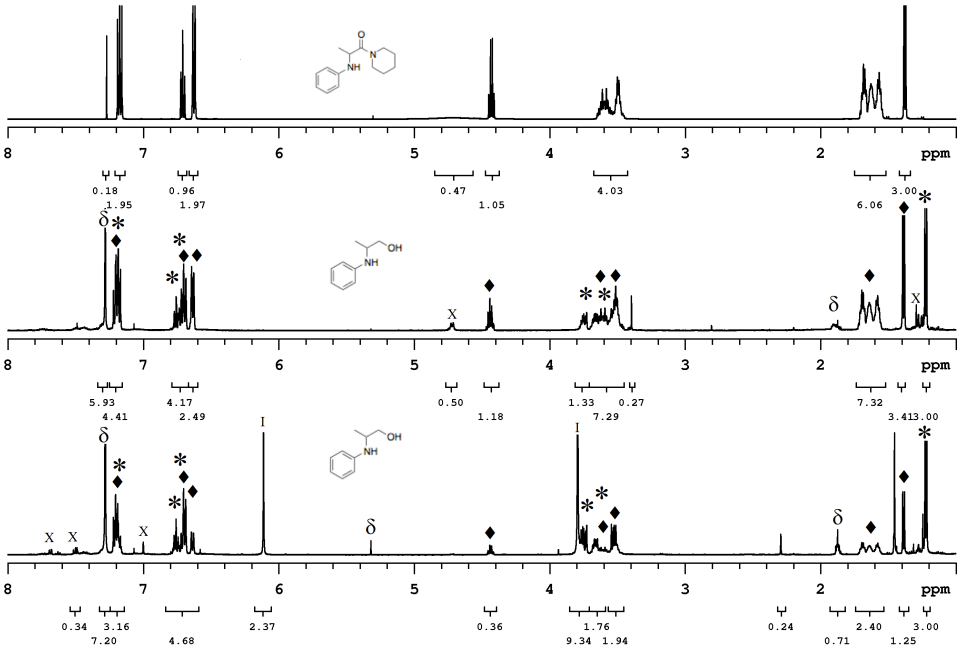


Figure S37. The δ region from 9 to 0.5 ppm showing the major products obtained from the hydrogenation of 2-phenoxy-2-(2-pyridyl)-1-(1-piperidinyl)-ethanone with the starting material. (α = formylpiperidine, φ = 2-(phenoxymethyl)pyridine)

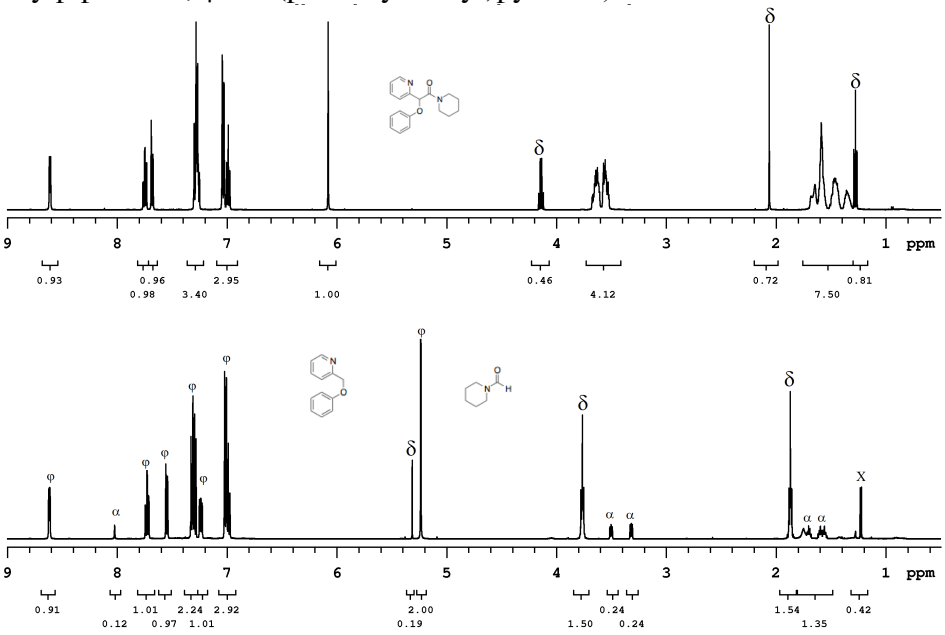


Figure S38. The δ region from 8 to 1 ppm, showing the comparison of the major alcohol product obtained from the hydrogenation of 2-phenylthio-1-(1-piperidinyl)-1-propanone (Confirmed by GC-MS) with the starting material and unidentified products.

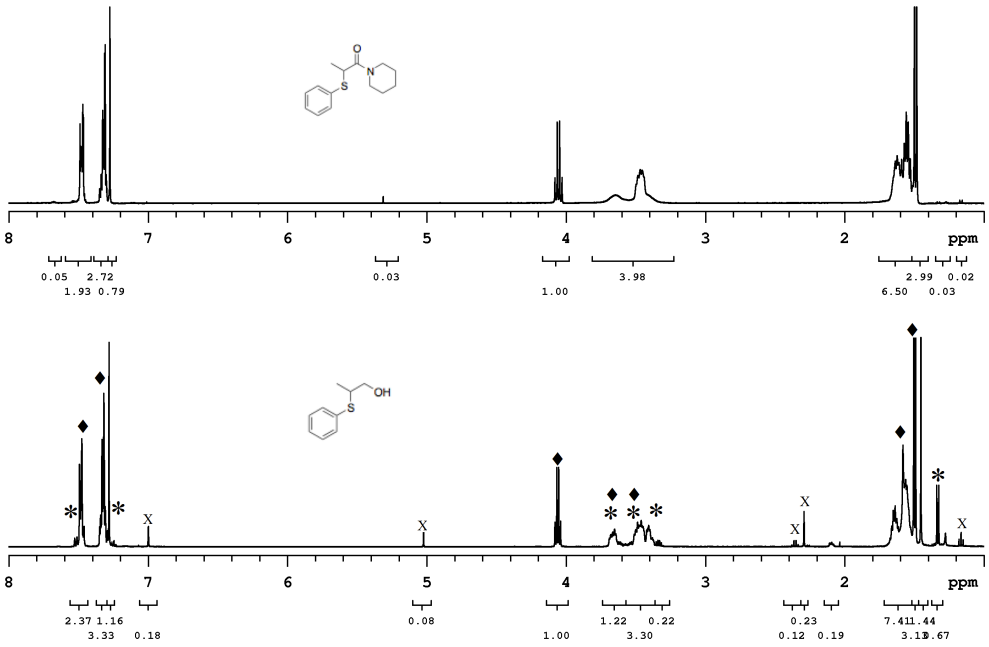


Figure S39. The δ region from 8 to 1 ppm, showing the comparison of the major alcohol product obtained from the hydrogenation of isopropyl 2-phenoxypropanoate with the starting material.

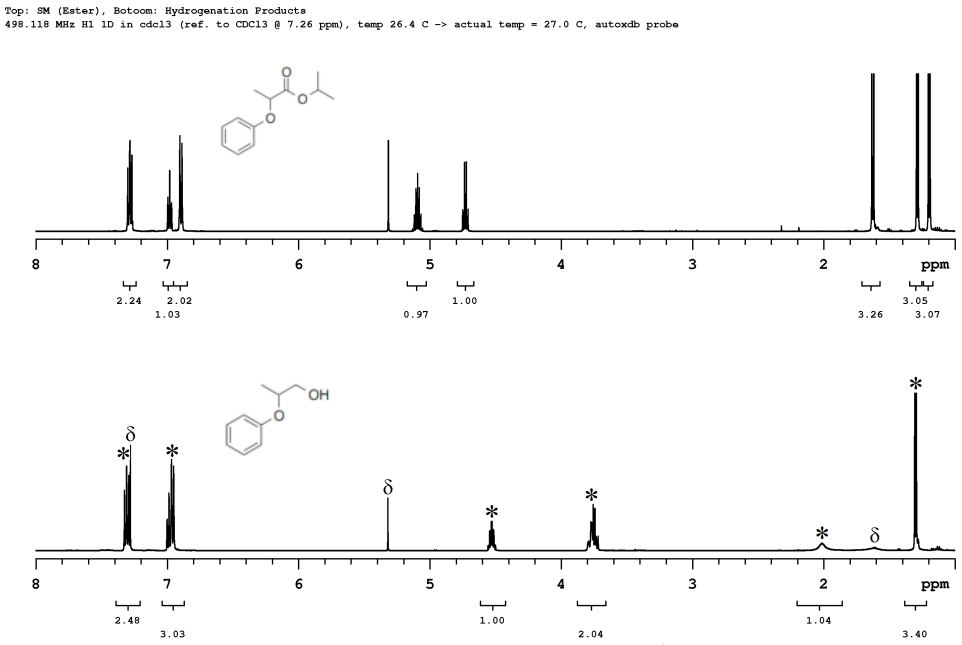


Figure S40. The δ region from 10 to 1 ppm, showing the comparison of the major alcohol product obtained from the hydrogenation of 2-phenoxypropanaldehyde with the starting material.

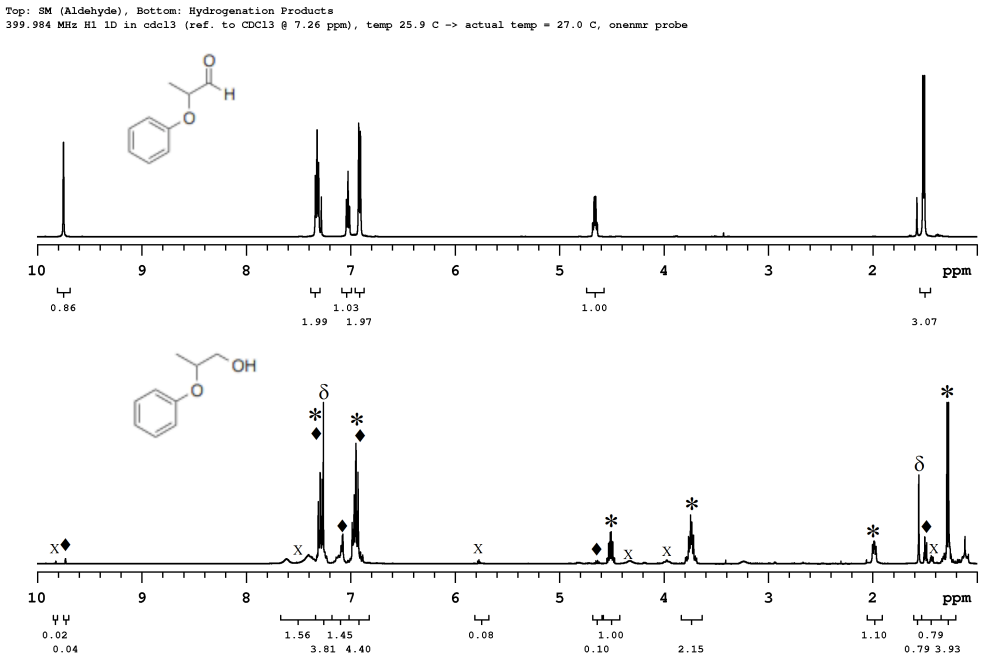


Figure S41. The δ region from 10 to 1 ppm showing major products obtained from the reduction of 2-phenoxy-1-(1-piperidinyl)-1-propanone by $LiAlH_4$. (Table 1, entry 9)

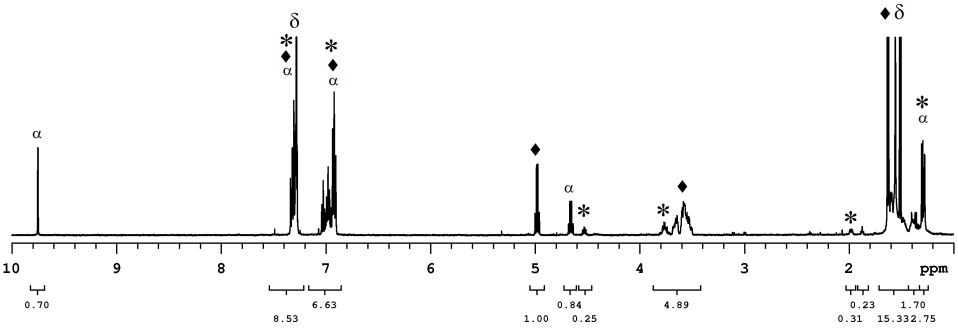


Figure S42. The δ region from 8 to 1 ppm, showing the major alcohol product obtained from the high turn over hydrogenation of 2-(4-fluorophenoxy)-1-(1-piperidinyl)-1-propanone at 50 atm H_2 pressure at room temperature.

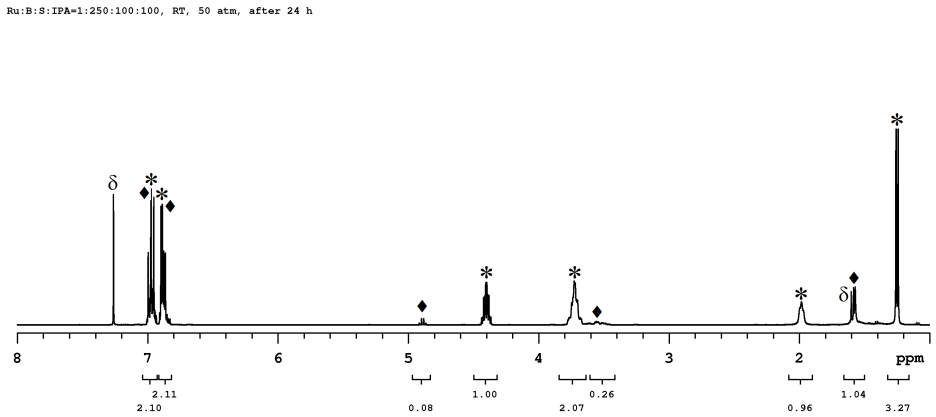


Figure S43. The δ region from 8 to 1 ppm showing the major alcohol product obtained from the hydrogenation of 2-phenoxy-1-(1-piperidinyl)-1-propanone after 4 h and 24 h.

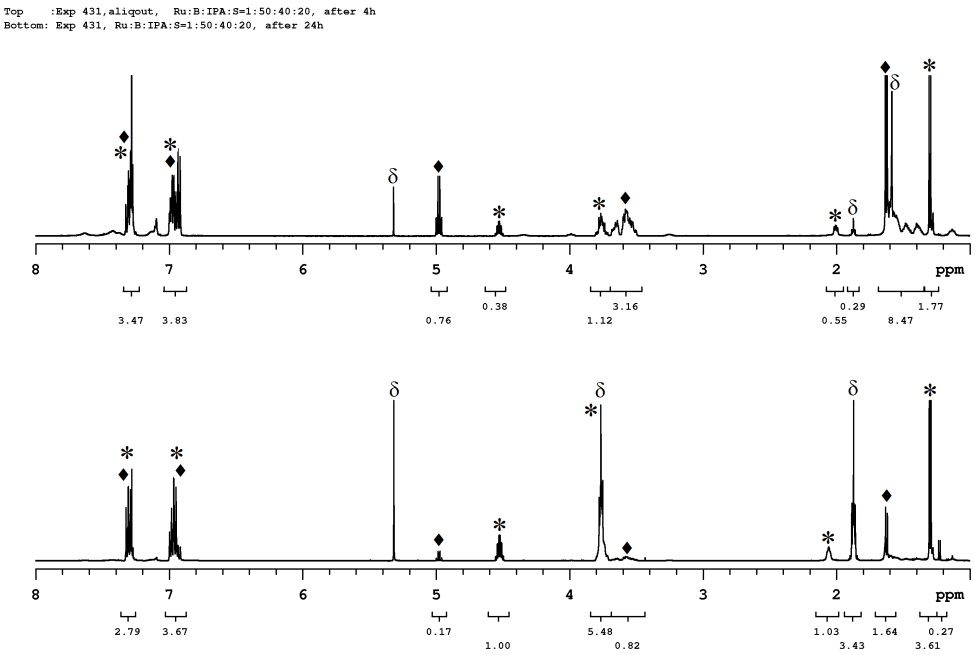
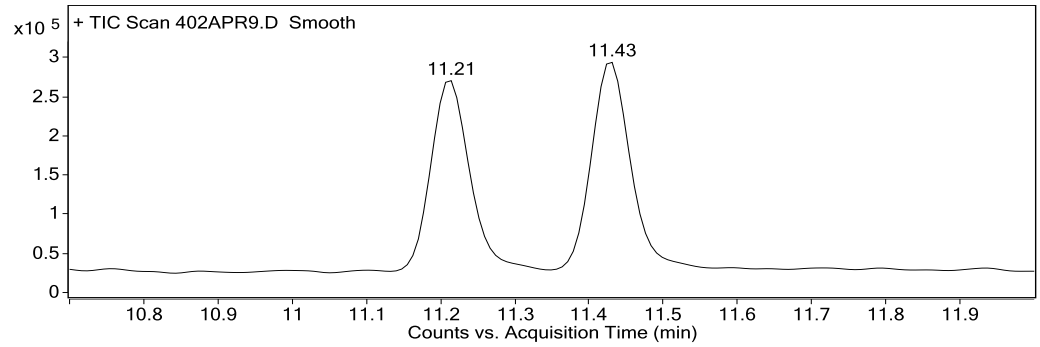
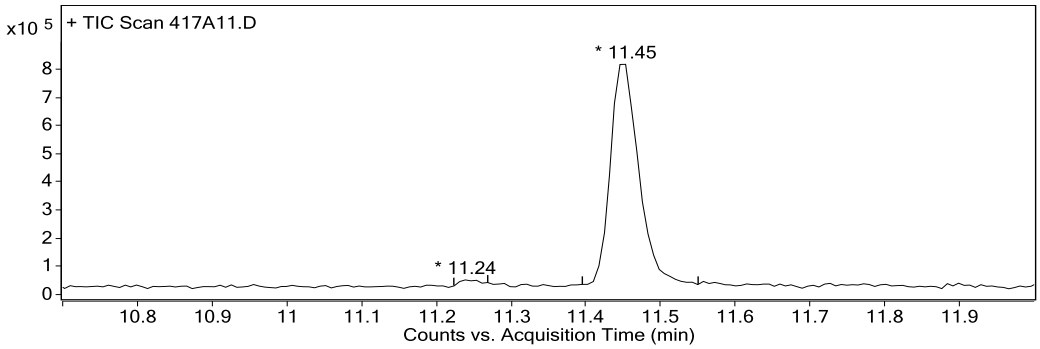


Figure S44. GC and HPLC traces of the racemic alcohol and the chiral alcohol obtained from the enantioselective hydrogenation.

2-phenoxypropan-1-ol. (entry 1)

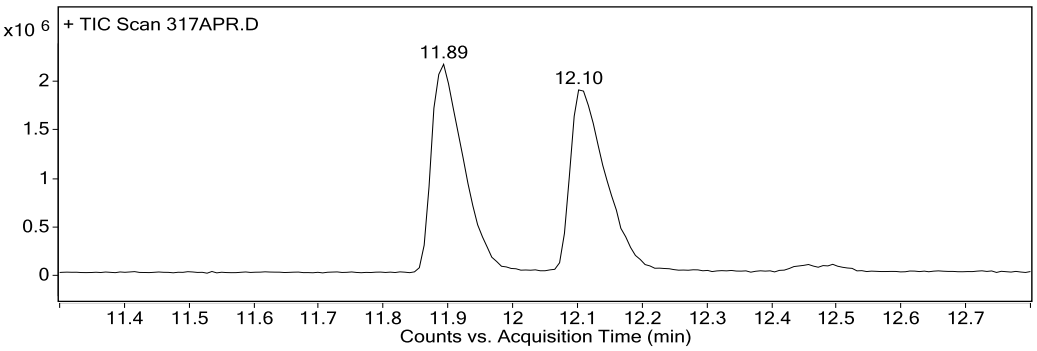


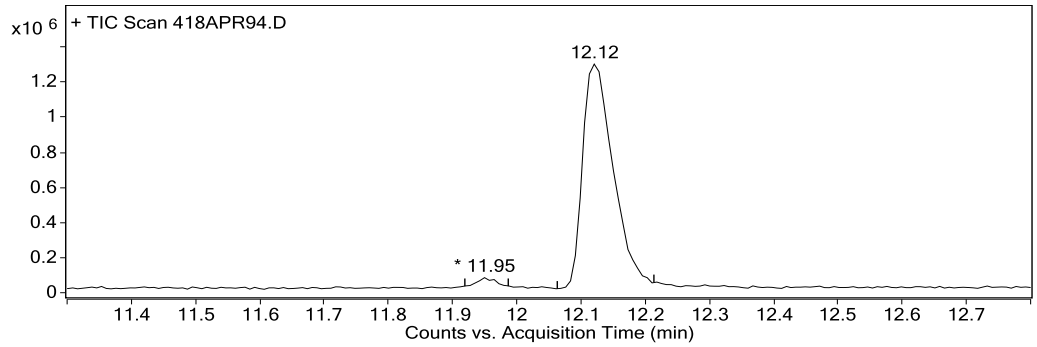


Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	11.22	11.24	11.27	17318	27069	1.3
2	11.4	11.45	11.55	780595	2078247	100

2-(4-fluorophenoxy)propan-1-ol (entry 2)

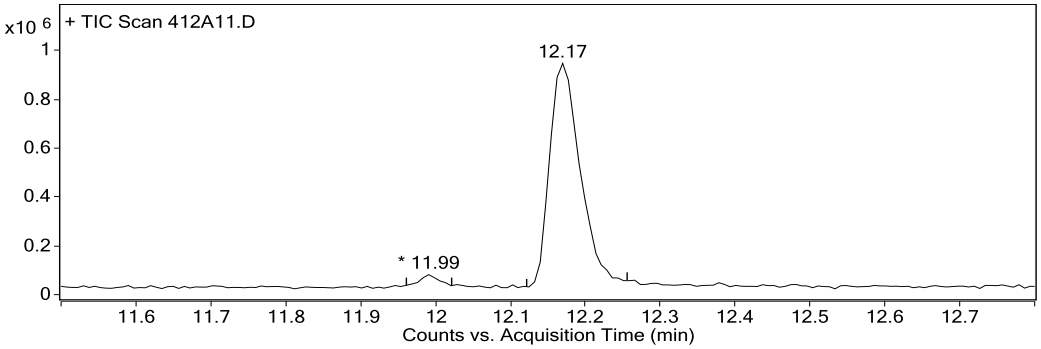




Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	11.92	11.95	11.99	47485	81373	1.92
2	12.06	12.12	12.21	1276924	4242469	100

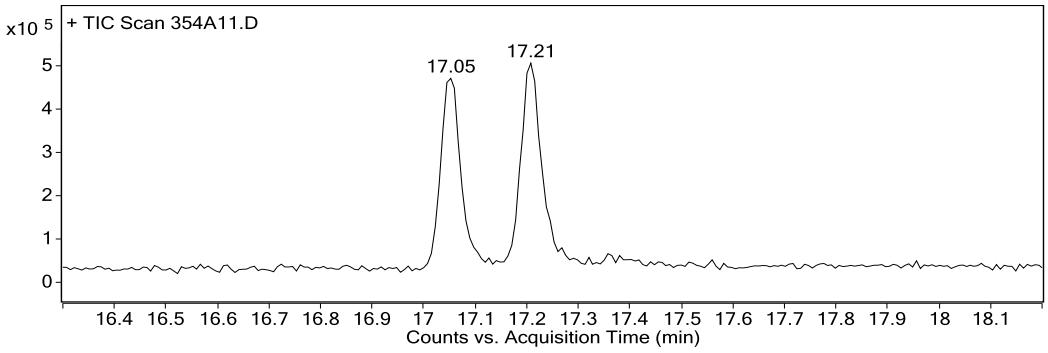
From the large-scale reaction (Table 2 of manuscript, entry 2, parenthesis**).**

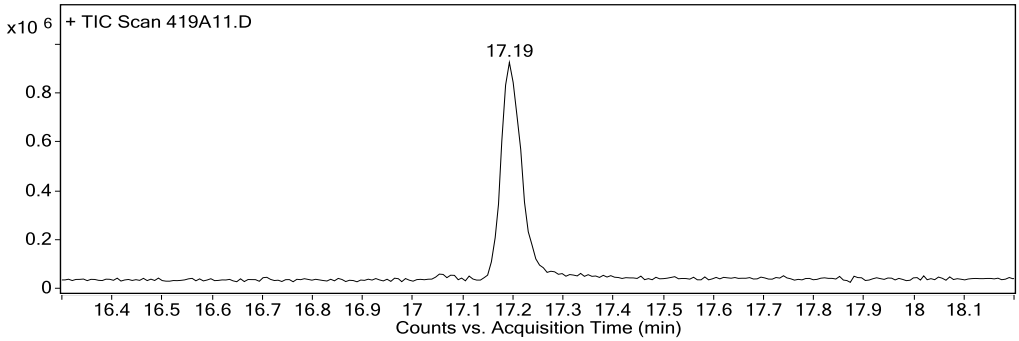


Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	11.96	11.99	12.02	44631	70408	2.68
2	12.12	12.17	12.26	915568	2630758	100

2-(4-chlorophenoxy)propan-1-ol (entry 3)

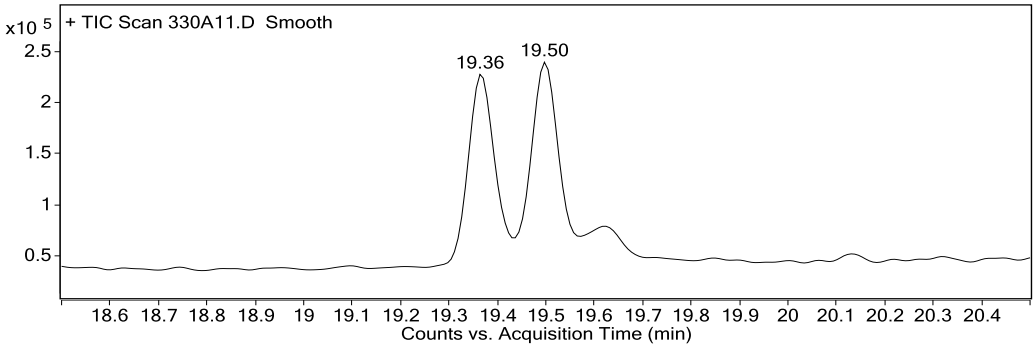


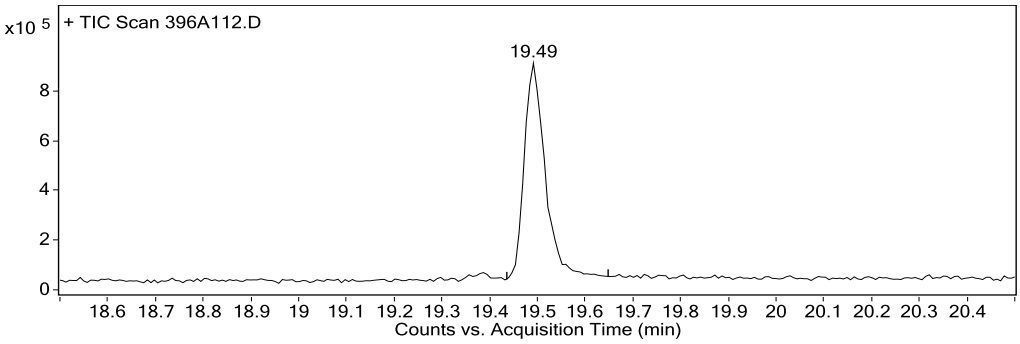


Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	17.14	17.19	17.37	887970.19	2628039.55	100

2-(4-bromophenoxy)propan-1-ol (entry 4)

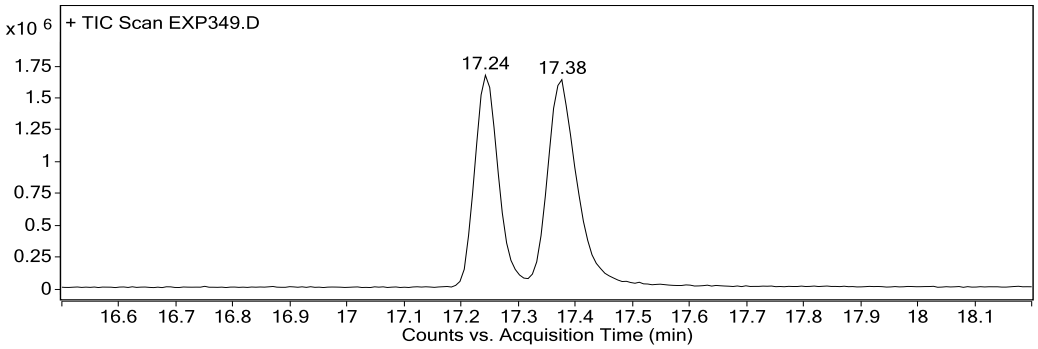


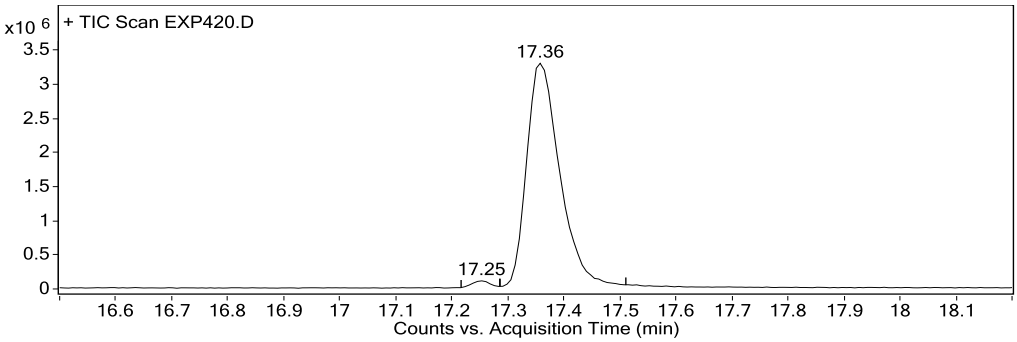


Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	19.44	19.49	19.65	866896.24	2674758.21	100

2-(4-methoxyphenoxy)propan-1-ol (entry 5)

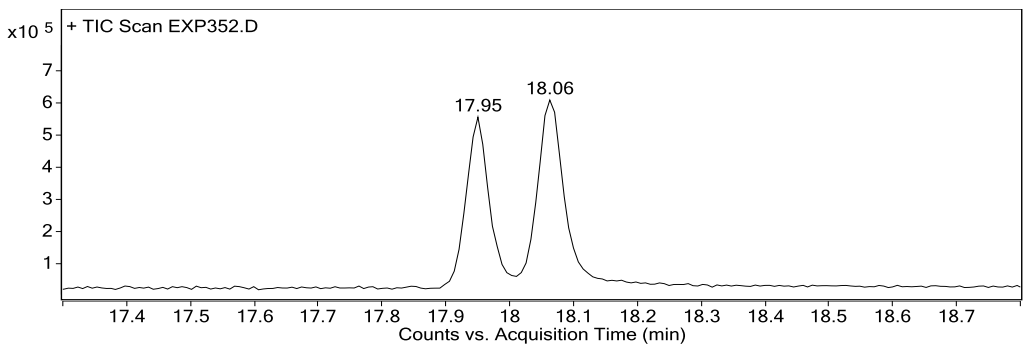


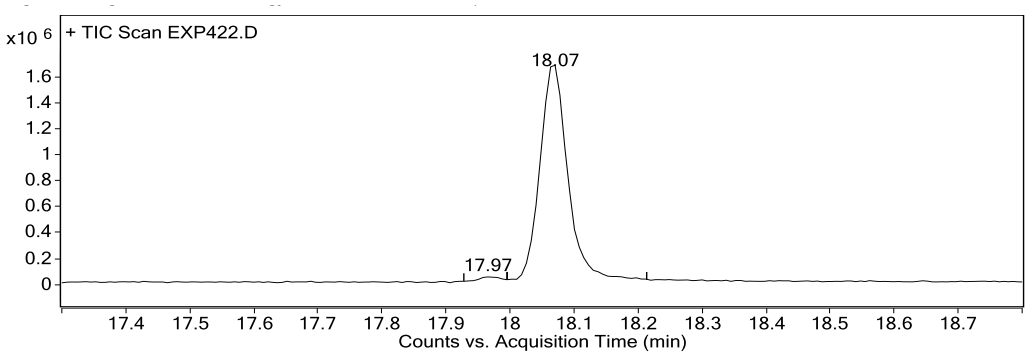


Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	17.22	17.25	17.29	97338	215728	1.6
2	17.29	17.36	17.51	3279112	13472025	100

2-(4-tert-butylphenoxy)propan-1-ol (entry 6)

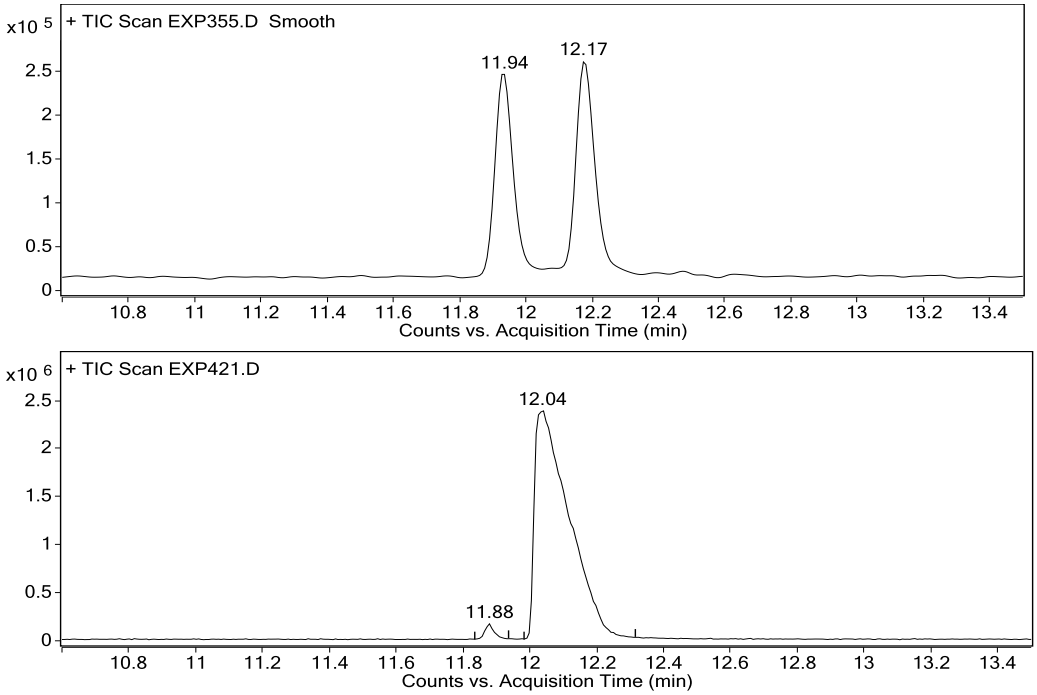




Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	17.93	17.97	18	33026.9	73723.86	1.42
2	18	18.07	18.21	1672424.66	5179617.21	100

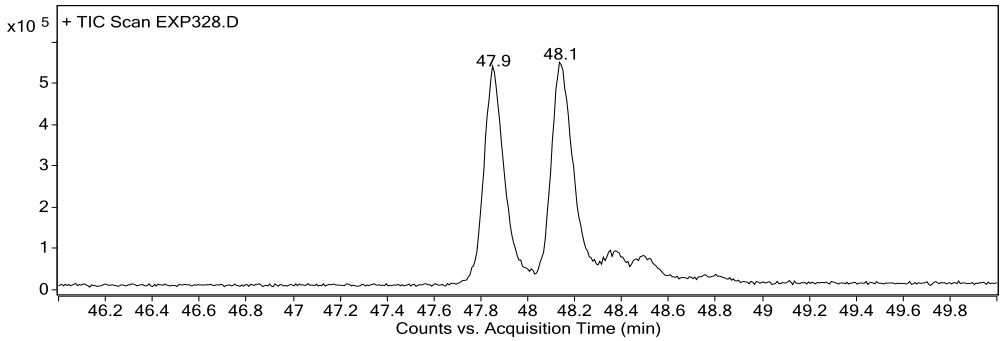
2-(3-fluorophenoxy)propan-1-ol (entry 7)

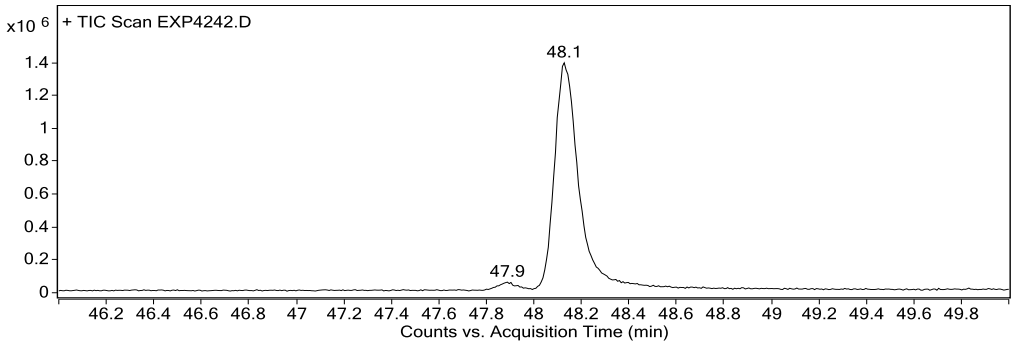


Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	11.83	11.88	11.93	159951	308217	1.81
2	11.98	12.04	12.32	2382693	17016646	100

2-(naphthalene-2-yloxy)propan-1-ol (entry 8)

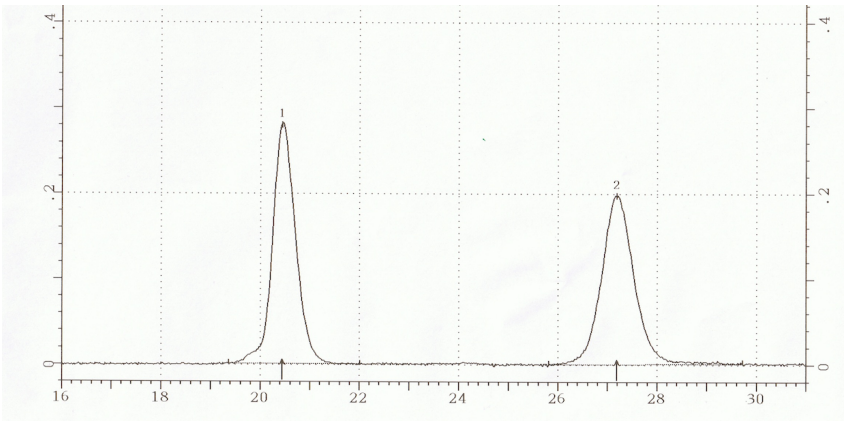


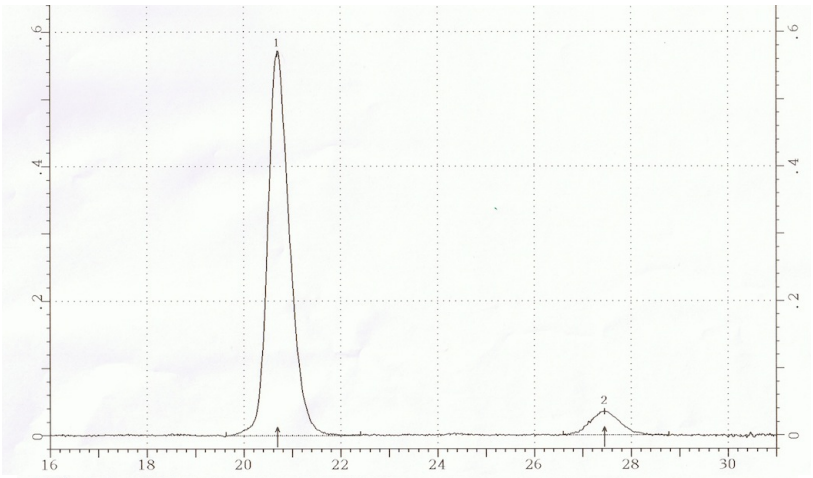


Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	47.8	47.9	48	41526.39	186124.47	1.89
2	48	48.1	48.5	1374170.32	9861774.68	100

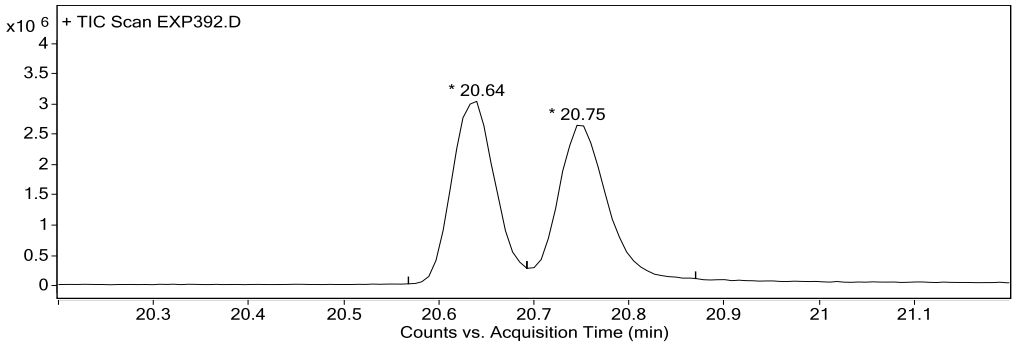
2-Phenoxy-2-phenylethyl alcohol (entry 9)

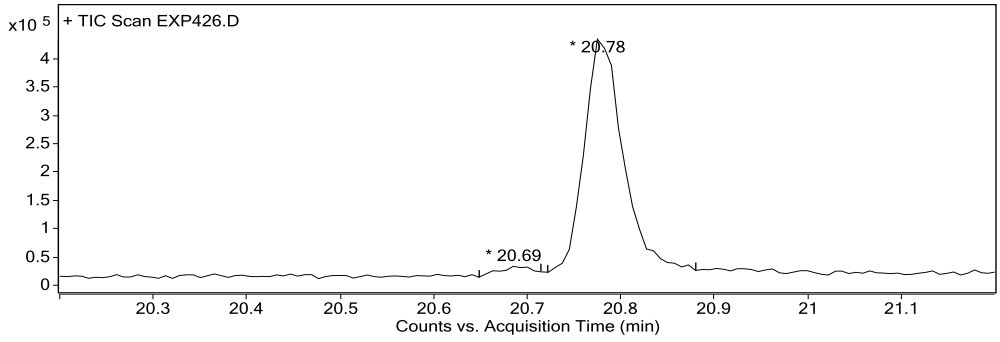




No.	Retention time	Height [AU]	Left time	Right time	Area [AU*min]	Area [%]
1	20.68	0.5682	19.63	22.41	0.300924	92.032
2	27.45	0.0353	26.60	28.77	0.026053	7.968

2-(4-bromophenoxy)butan-1-ol (entry 10)



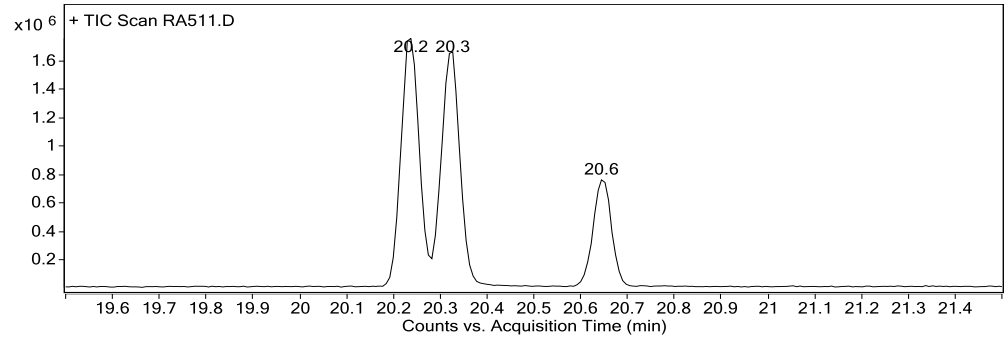


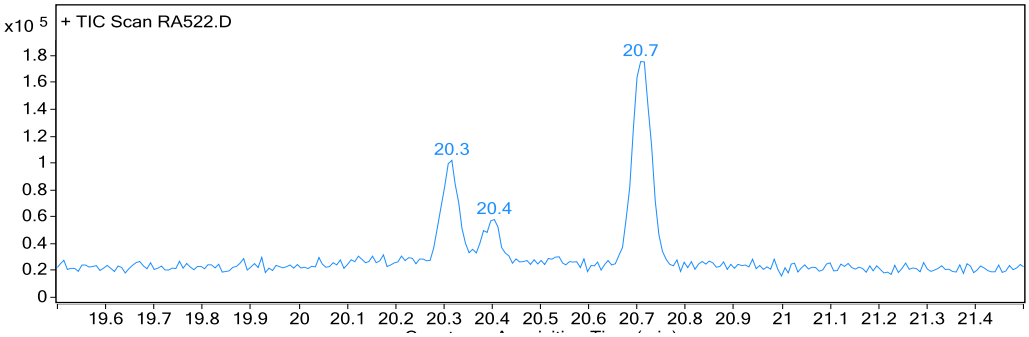
Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	20.65	20.69	20.72	14087	32395	2.74
2	20.72	20.78	20.88	409563	1183545	100

2-methoxypropyl benzoate (entry 11)

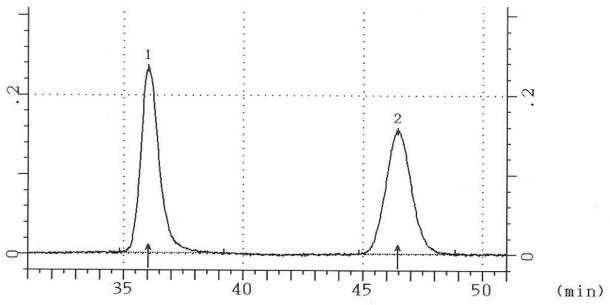
(The peak at 20.6 min corresponds to butylated hydroxytoluene (BHT) from the solvent, THF).

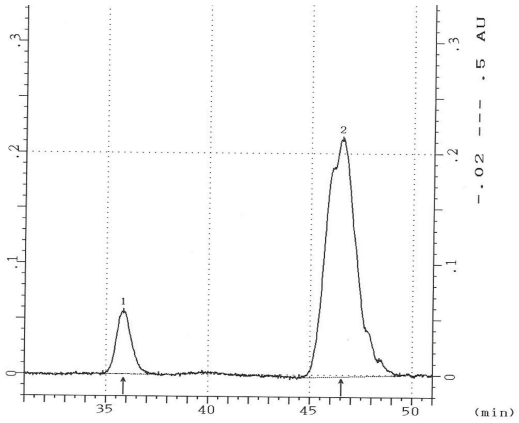




Peak	Start	RT	End	Height	Area	Area %
1	20.3	20.3	20.4	75678.48	194585.67	46.52
2	20.4	20.4	20.4	31503.01	76377.33	18.26
3	20.7	20.7	20.8	150078.95	418266.3	100

2-anilino-1-propanol (entry 12)





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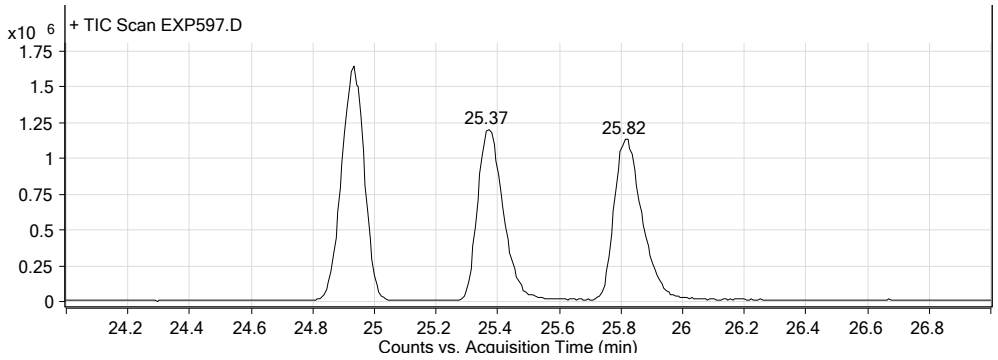
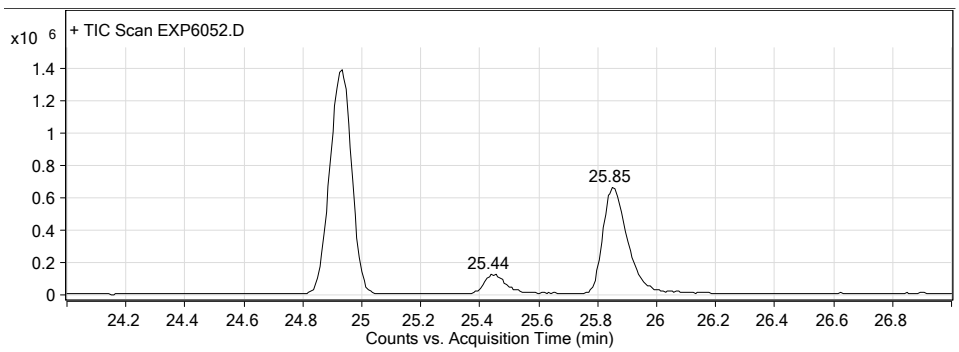
210 nm

No.	Retention time	Height [AU]	Left time	Right time	Area [AU*min]	Area [%]	Mark
1	35.84	0.0573	34.85	37.56	0.049986	12.020	I
2	46.52	0.2146	44.49	49.39	0.365882	87.980	I

2-(Phenylthio)-1-propanol (entry 14)

(The peak at 24.9 min corresponds to butylated hydroxytoluene (BHT) from the solvent, THF).



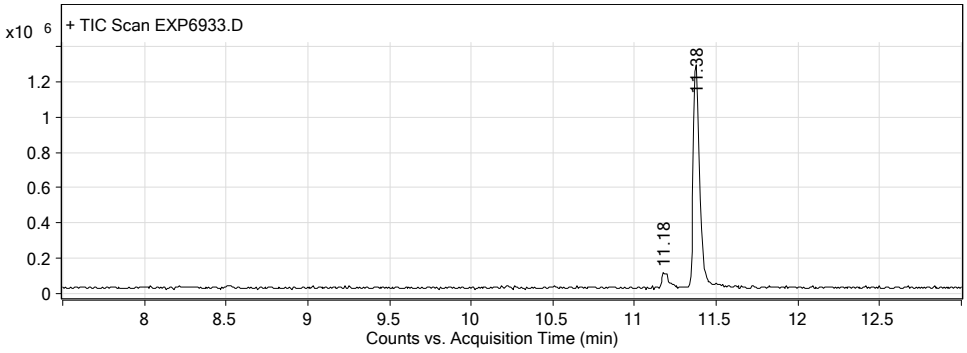


Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	25.37	25.44	25.6	115169.67	580341.35	15.13
2	25.75	25.85	26.15	652478.96	3835166.7	100

Figure S45. GC traces of the 2-phenoxypropan-1-ol obtained from the enantioselective hydrogenation of **13** with a reduced amount of base (Table 1, entry 9).

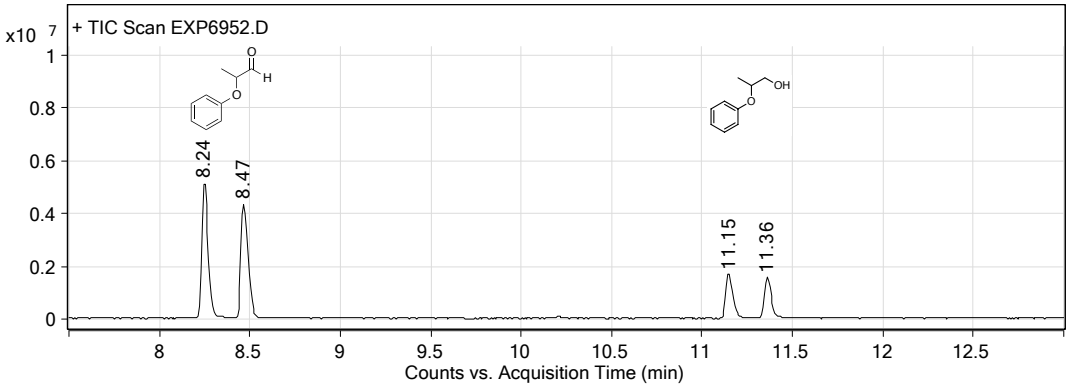
2-phenoxypropan-1-ol (Hydrogenation product)



Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	11.15	11.18	11.24	79011.05	195020.84	5.98
2	11.33	11.38	11.51	1249701.22	3262798.08	100

2-phenoxypropan-1-ol ($LiAlH_4$ reduction products from the unreactive **13**)



Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	8.2	8.24	8.39	5073344.52	13092169.26	100
2	8.42	8.47	8.6	4282989.21	11528082.91	88.05
3	11.1	11.15	11.29	1651794.27	4491239.55	34.3
4	11.32	11.36	11.49	1520308.17	4052818.41	30.96

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