Electronic supplementary information

Enhancement of Enantioselectivity by Alcohol Additives in Asymmetric Hydrogenation with Bis(oxazolinyl)phenyl Ruthenium Catalysts

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Contents

1. General Information.

^{1}H and ^{13}C NMR spectra were obtained at 25 ˚C on a Varian Mercury 300 spectrometer. ^{1}H NMR chemical shifts were reported in δ units, in ppm relative to the singlet at 7.26 ppm for $CDCl_3$ and 7.16 ppm for C_6D_6. ^{13}C NMR spectra were reported in terms of chemical shift (δ,

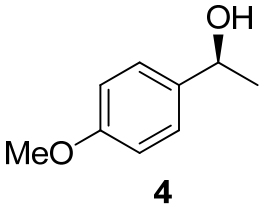
ppm) relative to the triplet at δ = 77.0 ppm for $CDCl_3$ and 128.0 ppm for C_6D_6. Infrared spectra were recorded on a JASCO FT/IR-230 spectrometer. Column chromatography was performed with a silica gel column (Kanto Kagaku, Silica gel 60). **1a** and **1b** were prepared by the reported method.[S1] Chiral alcohols **6-9** were purchased from Aldrich and used without further purification. Optically pure **5-(*S*)** and **5-(*R*)** (>99% ee) were prepared by hydrogenation of 9-acetylanthracene catalyzed by the (*S*,*S*)-phebox-Ru **1a** and the (*R*,*R*)-phebox-Ru **1a'**. Ether **12-(*S*)** was prepared from **5-(*S*)** by the reported method.[S2]

2. General procedures for hydrogenation.

A stainless steel autoclave was charged with **1a** (6.3 mg, 0.005 mmol), NaOMe (10.8 mg, 0.2 mmol), **5-(*S*)** (22.2 mg, 0.1 mmol) and ketone **2** (1.0 mmol). After addition of 2-propanol (10 mL) under an Ar atmosphere, the H_2 pressure was adjusted to 30 atm. The reaction mixture was stirred at 40 ºC for 24 h, and then the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel with ethyl acetate/*n*-hexane or ethyl acetate/toluene. Enantioselectivity of products was determined by using HPLC with a proper chiral column.

3. Characterization of 4, 7, 8, 24-31.

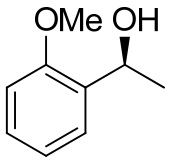
(*S*)-1-(4-methoxyphenyl)ethanol (Table 1, entry 4)



4

99% yield; 93% ee (*S*); HPLC analysis [Daicel Chiralpak AS-H, *n*-hexane/2-propanol = 95:5, 0.8 ml/min, 254 nm, t_R = 26.5, t_S = 34.1]; $[\alpha]_D^{24}$ –48.1 (c 1.0, $CHCl_3$); Lit.[S3]: $[\alpha]_D^{25}$ +53.5 (c 1.7, $CHCl_3$), 94% ee (*R*); ^{1}H NMR (300 MHz, $CDCl_3$, rt): δ = 1.49 (d, *J* = 6.5 Hz, 3H), 1.71 (brs, 1H), 3.81 (s, 3H), 4.87 (q, *J* = 6.5 Hz, 1H), 6.87-6.91 (m, 2H), 7.28-7.33 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, rt): δ = 25.1, 55.2, 69.7, 113.5, 126.4, 137.8, 158.4.

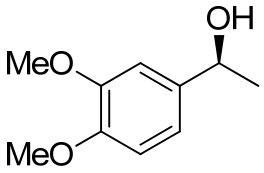
(*S*)-1-(2-methoxyphenyl)ethanol (Table 2, entry 1)



24

99% yield; 88% ee (*S*); HPLC analysis [Daicel Chiralcel OB-H, *n*-hexane/2-propanol = 95:5, 0.8 ml/min, 254 nm, t_S = 12.8, t_R = 23.8]; $[\alpha]_D^{23}$ = –25.1 (c 1.1, $CHCl_3$); Lit.[S4]: $[\alpha]_D^{20}$ +32.3 (c 2.0, $CHCl_3$), 94% ee (*R*); ^{1}H NMR (300 MHz, $CDCl_3$, rt): δ = 1.52 (d, *J* = 6.6 Hz, 3H), 3.88 (s, 3H), 5.10 (q, *J* = 6.6 Hz, 1H), 6.89 (d, *J* = 8.1 Hz, 1H), 6.94-6.99 (m, 1H), 7.23-7.28 (m, 1H), 7.32-7.35 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, rt): δ = 23.0, 55.2, 66.4, 110.2, 120.5, 125.8, 128.0, 133.2, 156.1.

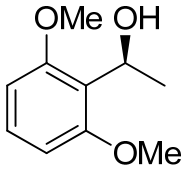
(*S*)-1-(3,4-dimethoxyphenyl)ethanol (Table 2, entry 2)



25

98% yield; 86% ee; HPLC [Daicel Chiralpak AS-H, *n*-hexane/2-propanol = 90:10, 1.0 ml/min, 240 nm, t_S = 17.9, t_R = 25.5]; $[\alpha]_D^{19}$ = –37.3 (c 0.99, $CHCl_3$); Lit.[S5]: $[\alpha]_D^{23}$ +43.0 (c 1.0, $CHCl_3$), 97% ee (*R*); ^{1}H NMR (300 MHz, $CDCl_3$, rt): δ = 1.43 (d, *J* = 6.4 Hz, 3H), 2.45 (brs, 1H), 3.82 (s, 3H), 3.83 (s, 3H), 4.77 (q, *J* = 6.4 Hz, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.82 (dd, *J* = 2.0, 8.1 Hz, 1H), 6.88 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, rt): δ = 25.1, 55.7, 55.8, 69.9, 108.3, 110.6, 117.1, 138.2, 147.7, 148.4.

(–)-1-(2,6-dimethoxyphenyl)ethanol (Table 2, entry 3)

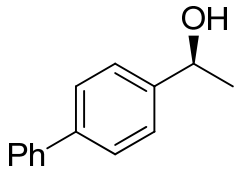


26

81% yield; 93% ee; HPLC [Daicel Chiralcel OZ-H, *n*-hexane/2-propanol = 90:10, 1.0 ml/min, 230 nm, t_{minor} = 11.5, t_{major} = 16.7]; $[\alpha]_D^{18}$ = –12.2 (c 0.99, $CHCl_3$); ^{1}H NMR (300 MHz,

$CDCl_3$, rt): δ = 1.49 (d, *J* = 6.8 Hz,, 3H), 3.84 (s, 6H), 3.91 (d, *J* = 11.4 Hz, 1H), 5.33 (dq, *J* = 11.4, 6.8 Hz, 1H), 6.56 (d, *J* = 8.5 Hz, 2H), 7.17 (t, *J* = 8.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, rt): δ = 23.6, 55.6, 63.9, 104.0, 120.5, 127.7, 156.9.

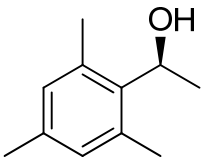
(*S*)-1-(p-Biphenyl)ethanol (Table 2, entry 4)



27

98% yield; 92% ee; HPLC [Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 95:5, 1.0 ml/min, 254 nm, t_S = 14.1, t_R = 15.7]; $[\alpha]_D^{22}$ = –41.9 (c 1.0, $CHCl_3$); Lit.[S6] gives $[\alpha]_D^{28}$ –43.7 (c 0.75, $CHCl_3$, 99% ee (*S*)); ^{1}H NMR (300 MHz, $CDCl_3$, rt): δ = 1.56 (d, *J* = 6.4 Hz, 3H), 1.89 (d, *J* = 3.0 Hz, 1H), 4.97 (dq, *J* = 3.0, 6.4 Hz, 1H), 7.32-7.49 (m, 5H), 7.56-7.63 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, rt): δ = 25.2, 69.9, 125.6, 126.7, 126.9, 126.9, 128.5, 139.9, 140.4, 144.5.

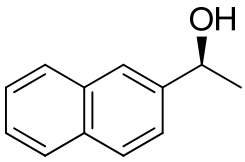
(*S*)-1-(2,4,6-trimethylphenyl)ethanol (Table 2, entry 5)



28

83% yield, 94% ee; HPLC [Daicel Chiralcel OD-H, *n*-hexane/2-propanol = 98:2, 1.0 ml/min, 220 nm, t_R = 15.6, t_S = 16.9]; $[\alpha]_D^{23}$ = –62.2 (c 1.0, $CHCl_3$); Lit.[S7] gives $[\alpha]_D^{20}$ +37.3 (c 0.50, $CHCl_3$, 77% ee (*R*)); ^{1}H NMR (300 MHz, $CDCl_3$, rt): δ = 1.54 (d, *J* = 6.7 Hz, 3H), 1.68 (br, 1H), 2.26 (s, 3H), 2.43 (s, 6H), 5.37 (dq, *J* = 3.4, 6.7 Hz, 1H), 6.83 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, rt): δ = 20.6, 20.8, 21.6, 67.2, 129.8, 135.3, 136.0, 137.3.

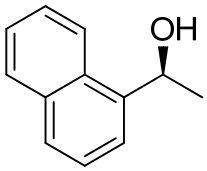
(*S*)-1-(2'-naphthyl)ethanol (Table 2, entry 6)



8

97% yield; 91% ee; HPLC [Daicel Chiralcel OJ-H, *n*-hexane/2-propanol = 95:5, 0.8 ml/min, 254 nm, t_S = 39.3, t_R = 54.4]; $[\alpha]_D^{23}$ = –46.1 (c 1.0, $CHCl_3$); Lit.[S8] gives $[\alpha]_D^{25}$ +41.2 (c 0.50, EtOH, 95% ee (*R*)); ^{1}H NMR (300 MHz, $CDCl_3$, rt): δ = 1.60 (d, *J* = 6.3 Hz, 3H), 1.66 (br, 1H), 5.09 (q, *J* = 6.3 Hz, 1H), 7.44-7.53 (m, 3H), 7.82-7.86 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, rt): δ = 25.1, 70.0, 123.4, 123.5, 125.3, 125.7, 127.3, 127.6, 127.8, 132.4, 132.9, 142.8.

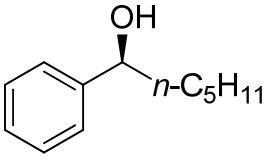
(*S*)-1-(2'-naphthyl)ethanol (Table 2, entry 7)



7

98% yield; 90% ee; HPLC [Daicel Chiralcel OD-H, *n*-hexane/2-propanol = 95:5, 1.0 ml/min, 283 nm, t_S = 19.8, t_R = 42.0]; $[\alpha]_D^{23}$ = –58.1 (c 1.1, $CHCl_3$); Lit.[S9] gives $[\alpha]_D^{25}$ +82.1 (c 1.0, ether, 99% ee (*R*)); ^{1}H NMR (300 MHz, $CDCl_3$, rt): δ = 1.69 (d, *J* = 6.5 Hz, 3H), 1.98 (d, *J* = 3.6 Hz, 1H), 5.69 (dq, *J* = 3.6, 6.5 Hz, 1H), 7.45-7.57 (m, 3H), 7.69 (d, *J* = 7.2 Hz, 1H), 7.78 (d, *J* = 8.7 Hz, 1H), 7.86-7.90 (m, 1H), 8.10-8.14 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, rt): δ = 24.5, 67.1, 121.7, 122.9, 125.3, 125.8, 127.7, 128.6, 130.0, 133.5, 141.1.

(*S*)-1-phenylhexanol (Table 2, entry 11)

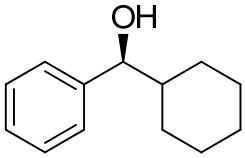


29

96% yield; 91% ee; HPLC [Daicel Chiralcel OB-H, *n*-hexane/2-propanol = 95:5, 1.0 ml/min,

254 nm, t_S = 7.2, t_R = 9.5]; $[\alpha]_D^{20}$ = –32.3 (c 1.0, $CHCl_3$); Lit.[S6] gives $[\alpha]_D^{24}$ –35.0 (c 0.88, $CHCl_3$, 92% ee (*S*)); ^{1}H NMR (300 MHz, $CDCl_3$, rt): δ = 0.86-0.91 (m, 3H), 1.20-1.50 (m, 6H), 1.62-1.90 (m, 3H), 4.67 (t, *J* = 6.5 Hz, 1H), 7.24-7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, rt): δ = 14.2, 22.7, 25.6, 31.8, 39.1, 74.5, 125.7, 127.1, 128.1, 144.6.

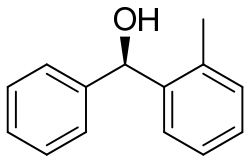
(*S*)-cyclohexyl(phenyl)methanol (Table 2, entry 13)



30

98% yield, 67% ee; HPLC [Daicel Chiralcel OD-H, *n*-hexane/2-propanol = 95:5, 1.0 ml/min, 220 nm, t_S = 9.2, t_R = 11.2]; $[\alpha]_D^{20}$ = –22.2 (c 1.0, $CHCl_3$); Lit.[S10] gives $[\alpha]_D^{23}$ +38.0 (c 0.4, $CHCl_3$, 96% ee (*R*)); ^{1}H NMR (300 MHz, $CDCl_3$, rt): δ = 0.87-1.32 (m, 5H), 1.34-1.43 (m, 1H), 1.56-1.83 (m, 4H), 1.88 (s, 1H), 1.96-2.04 (m, 1H), 4.37 (d, *J* = 7.2 Hz, 1H), 7.23-7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, rt): δ = 26.1, 26.2, 26.5, 28.9, 29.3, 44.9, 79.2, 126.4, 127.0, 127.8, 143.3.

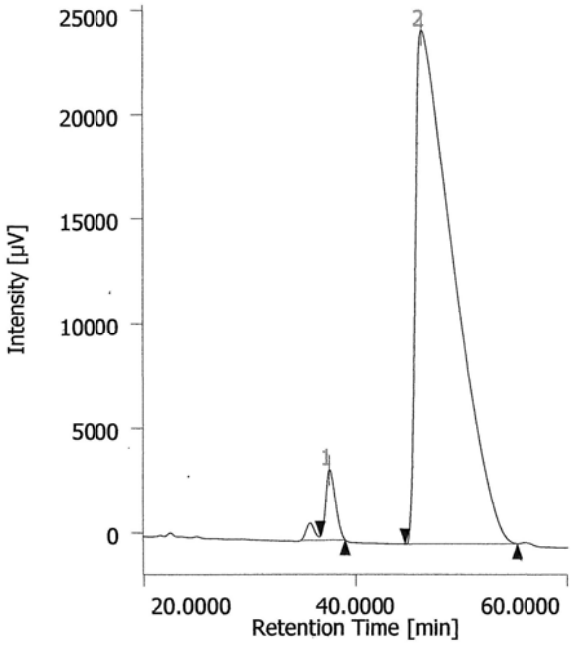
(*R*)-phenyl(2-tolyl)methanol (Table 2, entry 15)

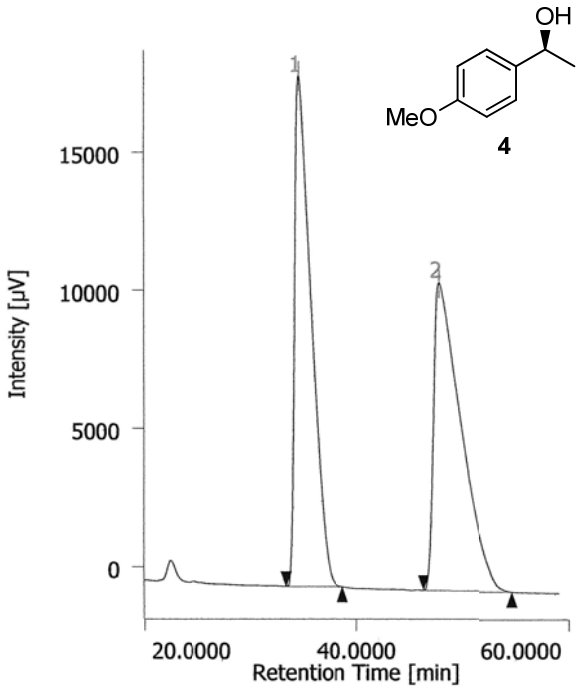


31

97% yield; 51% ee; HPLC [Daicel Chiralcel OJ-H, *n*-hexane/2-propanol = 95:5, 1.0 ml/min, 220 nm, t_S = 31.0, t_R = 34.8]; $[\alpha]_D^{23}$ = –4.3 (c 2.0, EtOH); Lit.[S11] gives $[\alpha]_D$ –7.5 (c 5.1, EtOH, 95% ee (*R*)); ^{1}H NMR (300 MHz, $CDCl_3$, rt): δ = 2.26 (s, 3H), 6.02(s, 1H), 7.13-7.36 (m, 8H), 7.53 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, rt): δ = 19.2, 72.8, 125.5, 126.6, 126.8, 126.9, 127.8, 129.9, 134.8, 140.9, 142.3.

4. HPLC charts of 4, 7, 8, 24-31.

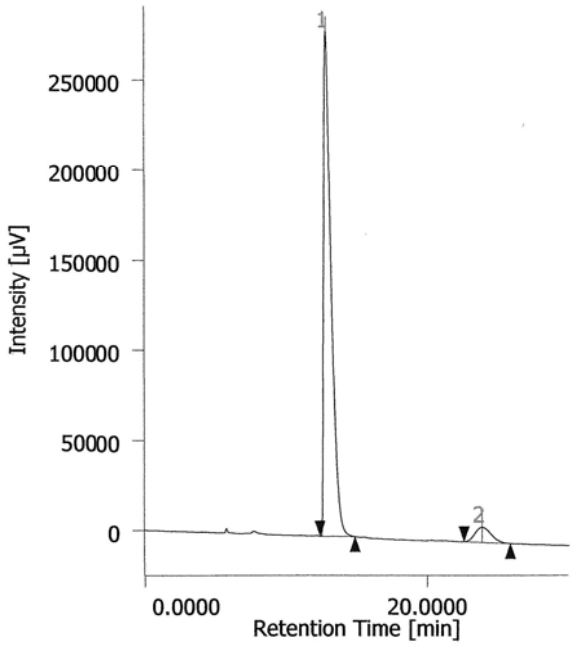


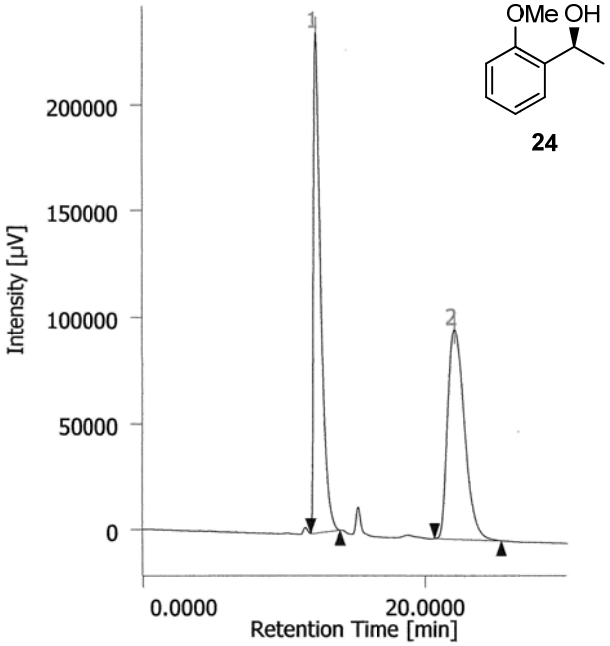


#	tR [min]	area [μV·sec]	area%
1	37.525	214866	3.419
2	46.233	6069539	96.581

#	tR [min]	area [μV·sec]	area%
1	34.492	1996873	49.896
2	47.783	2005227	50.104

Fig. S1 HPLC charts of **4**.

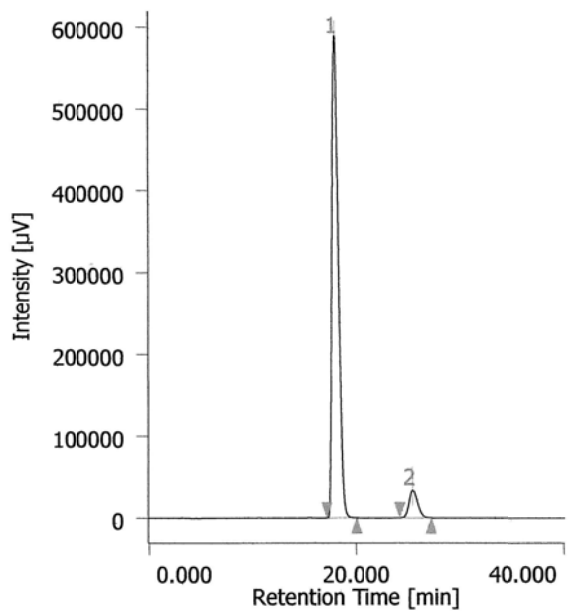




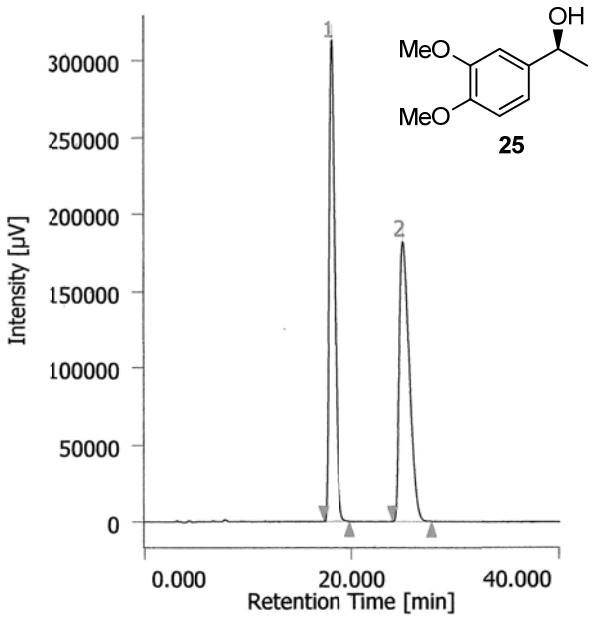
#	tR [min]	area [μV·sec]	area%
1	12.758	10334538	93.952
2	23.825	665220	6.048

#	tR [min]	area [μV·sec]	area%
1	12.200	8211688	49.929
2	22.058	8235092	50.071

Fig. S2 HPLC charts of **24**.

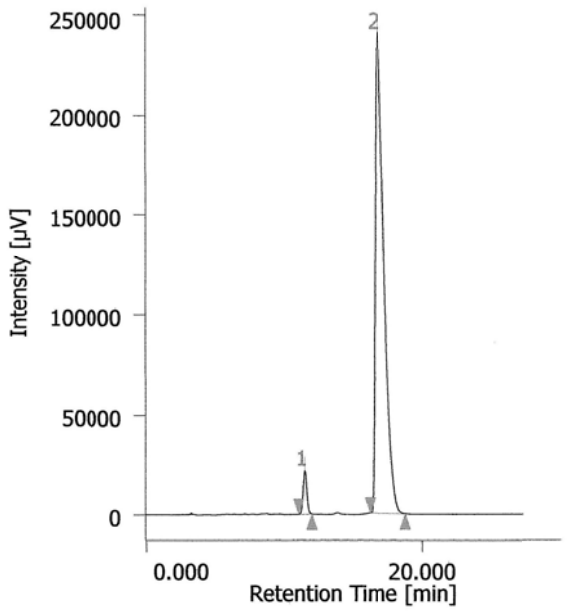


#	tR [min]	area [μV·sec]	area%
1	17.913	25291306	93.050
2	25.478	1889112	6.950

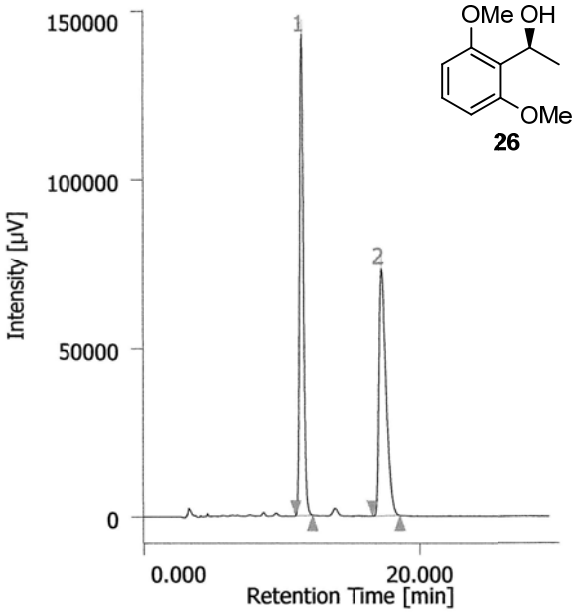


#	tR [min]	area [μV·sec]	area%
1	18.042	12103687	49.861
2	24.933	12170976	50.139

Fig. S3 HPLC charts of **25**.

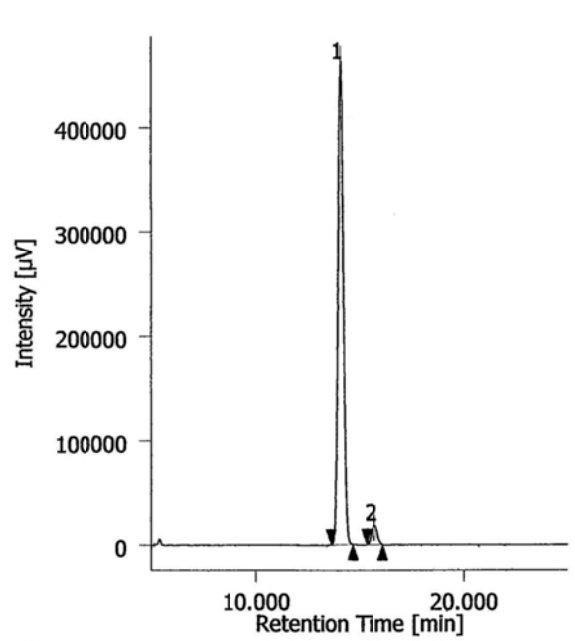


#	tR [min]	area [μV·sec]	area%
1	11.495	399456	3.513
2	16.725	10971287	96.487

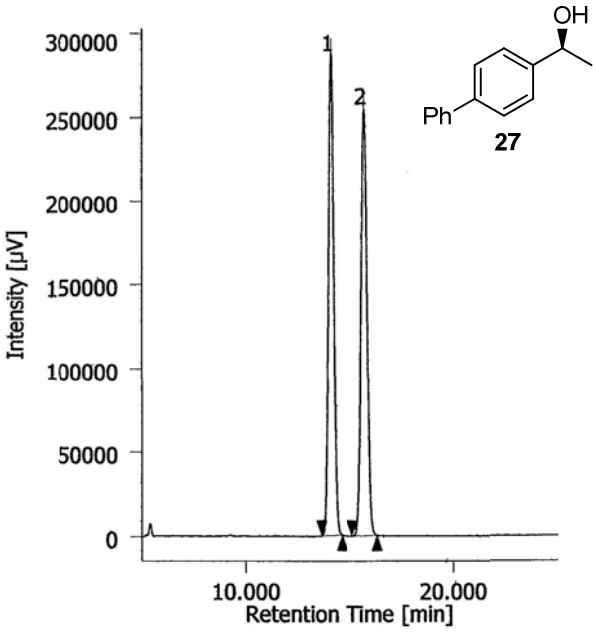


#	tR [min]	area [μV·sec]	area%
1	11.430	2754741	50.233
2	17.202	2729147	49.767

Fig. S4 HPLC charts of **26**.

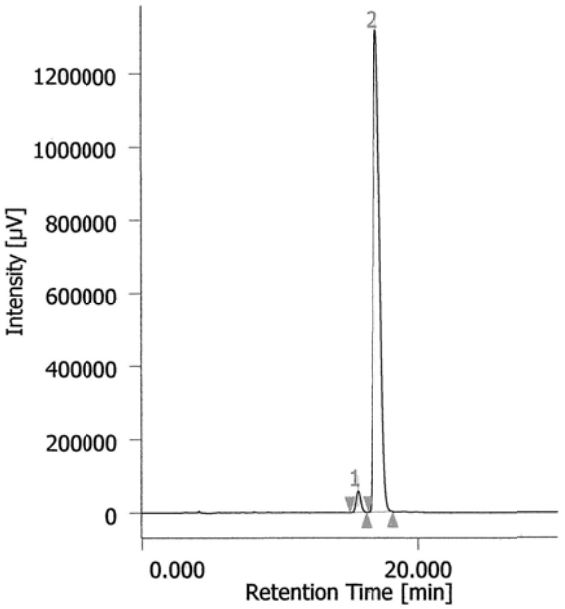


#	tR [min]	area [μV·sec]	area%
1	14.087	8150994	95.875
2	15.702	350733	4.125

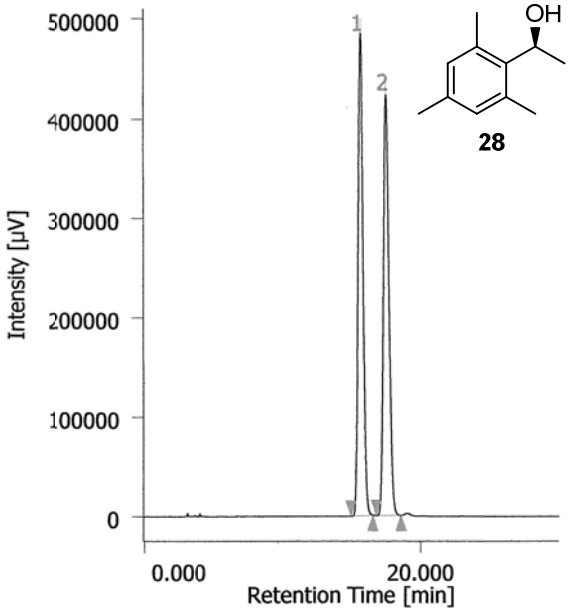


#	tR [min]	area [μV·sec]	area%
1	14.082	5046578	49.962
2	15.690	5054350	50.038

Fig. S5 HPLC charts of **27**.

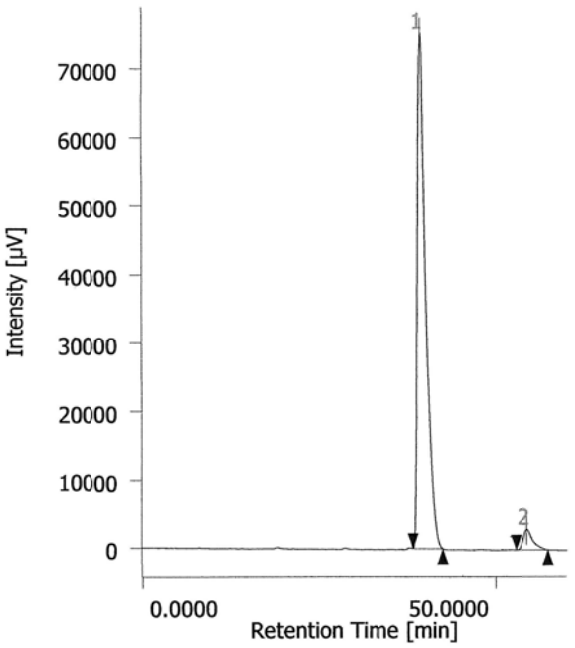


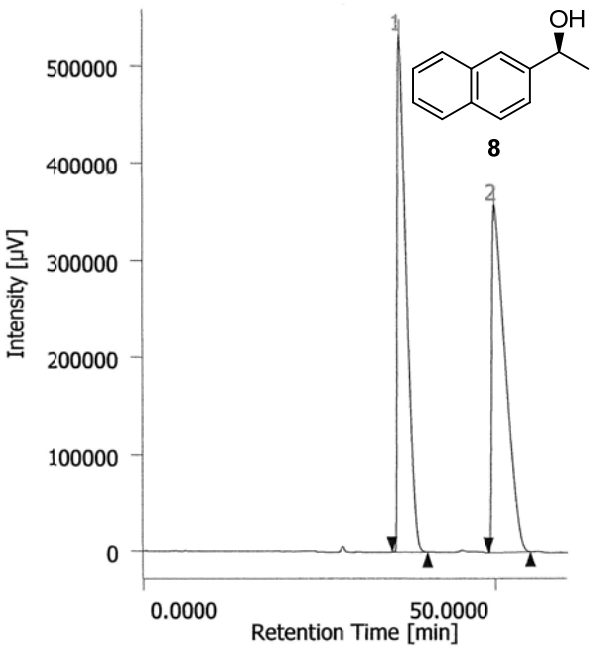
#	tR [min]	area [μV·sec]	area%
1	15.642	1333787	2.993
2	16.902	43228946	97.007



#	tR [min]	area [μV·sec]	area%
1	15.668	11884623	49.938
2	17.497	11913980	50.062

Fig. S6 HPLC charts of **28**.

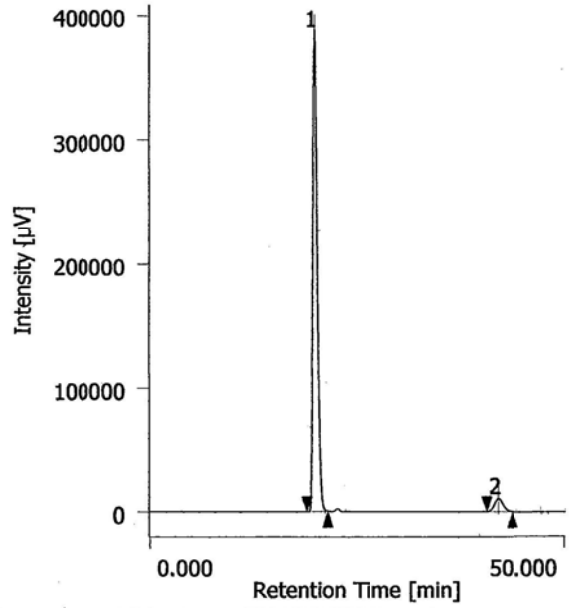


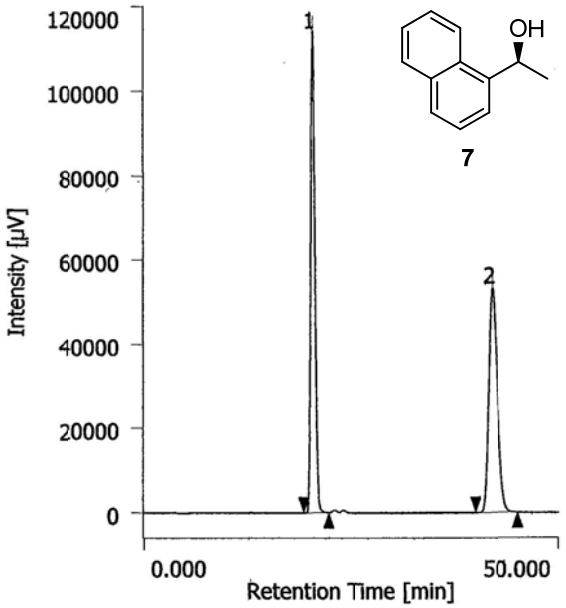


#	tR [min]	area [μV·sec]	area%
1	39.308	6149903	95.596
2	54.342	283315	4.404

#	tR [min]	area [μV·sec]	area%
1	36.200	46821926	49.977
2	49.750	46864956	50.023

Fig. S7 HPLC charts of **8**.

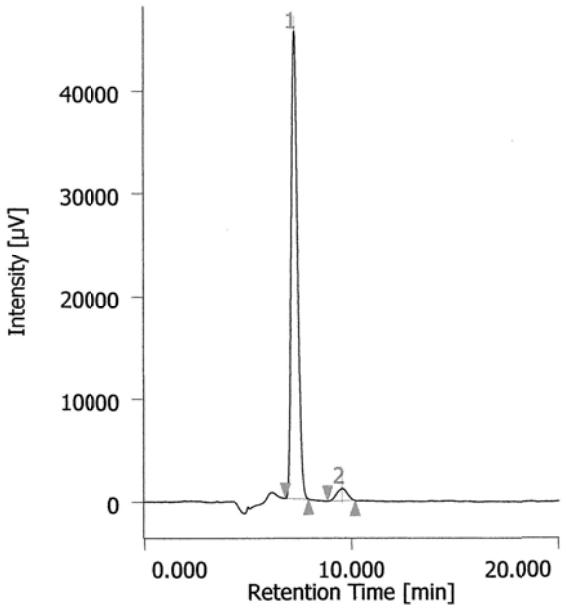




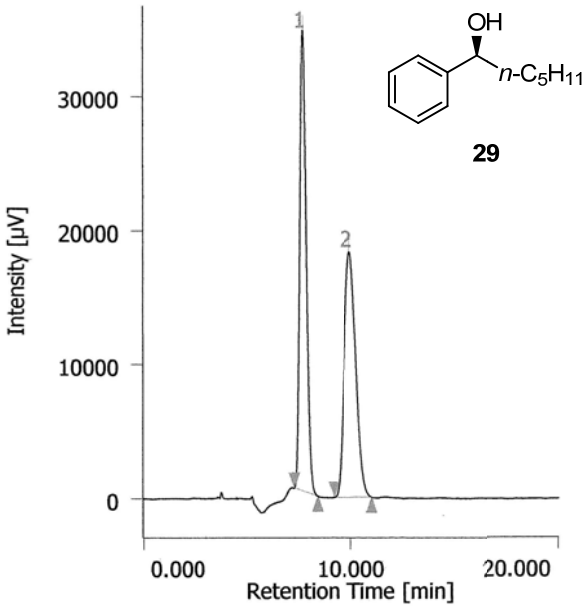
#	tR [min]	area [μV·sec]	area%
1	19.820	14242999	95.135
2	42.003	728307	4.865

#	tR [min]	area [μV·sec]	area%
1	20.317	3952583	50.032
2	42.092	3947519	49.968

Fig. S8 HPLC charts of **7**.

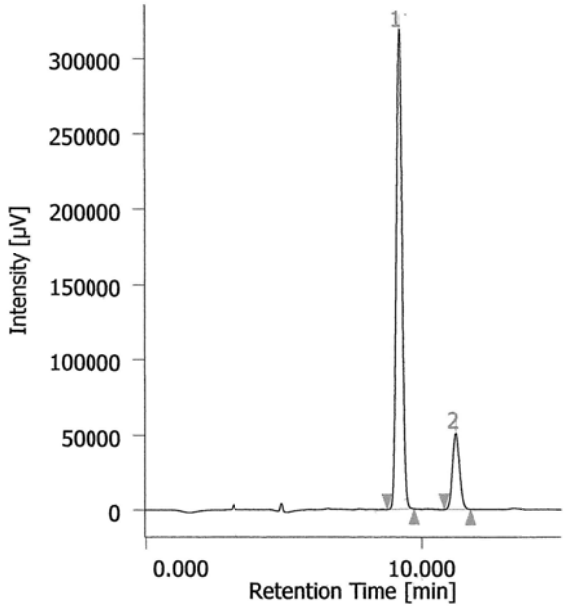


#	tR [min]	area [μV·sec]	area%
1	7.218	942210	95.720
2	9.552	42128	4.280

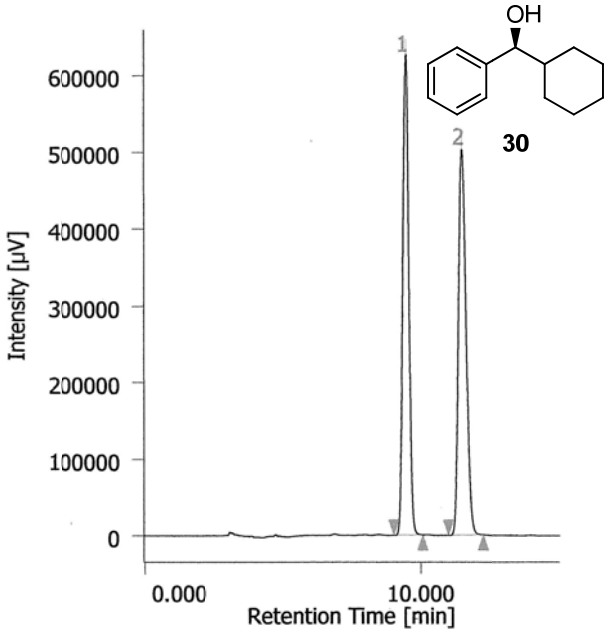


#	tR [min]	area [μV·sec]	area%
1	7.662	737426	50.737
2	9.922	716011	49.263

Fig. S9 HPLC charts of **29**.

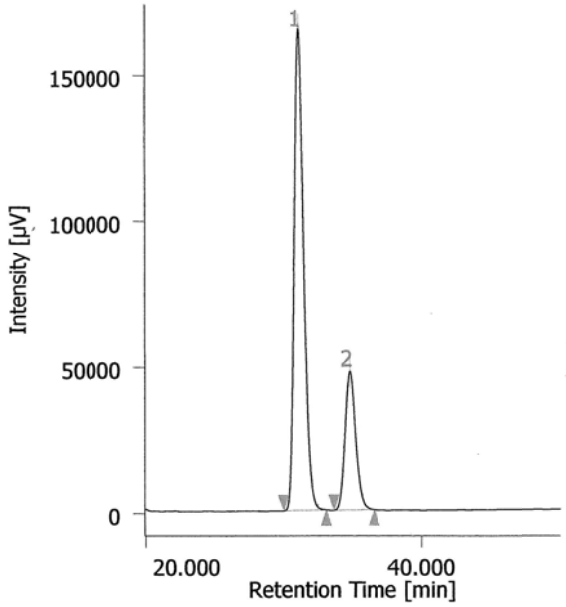


#	tR [min]	area [μV·sec]	area%
1	9.188	4548462	83.426
2	11.225	903636	16.574

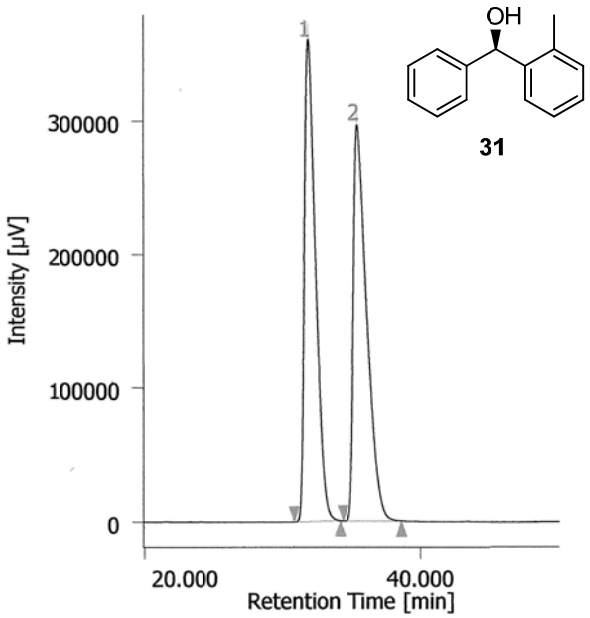


#	tR [min]	area [μV·sec]	area%
1	9.450	9342190	49.484
2	11.480	9537145	50.516

Fig. S10 HPLC charts of **30**.



#	tR [min]	area [μV·sec]	area%
1	31.033	7850547	75.437
2	34.765	2556202	24.563



#	tR [min]	area [μV·sec]	area%
1	31.823	19784491	49.957
2	35.408	19818902	50.043

Fig. S11 HPLC charts of **31**.

5. NMR spectra of 4, 7, 8, 24-31.

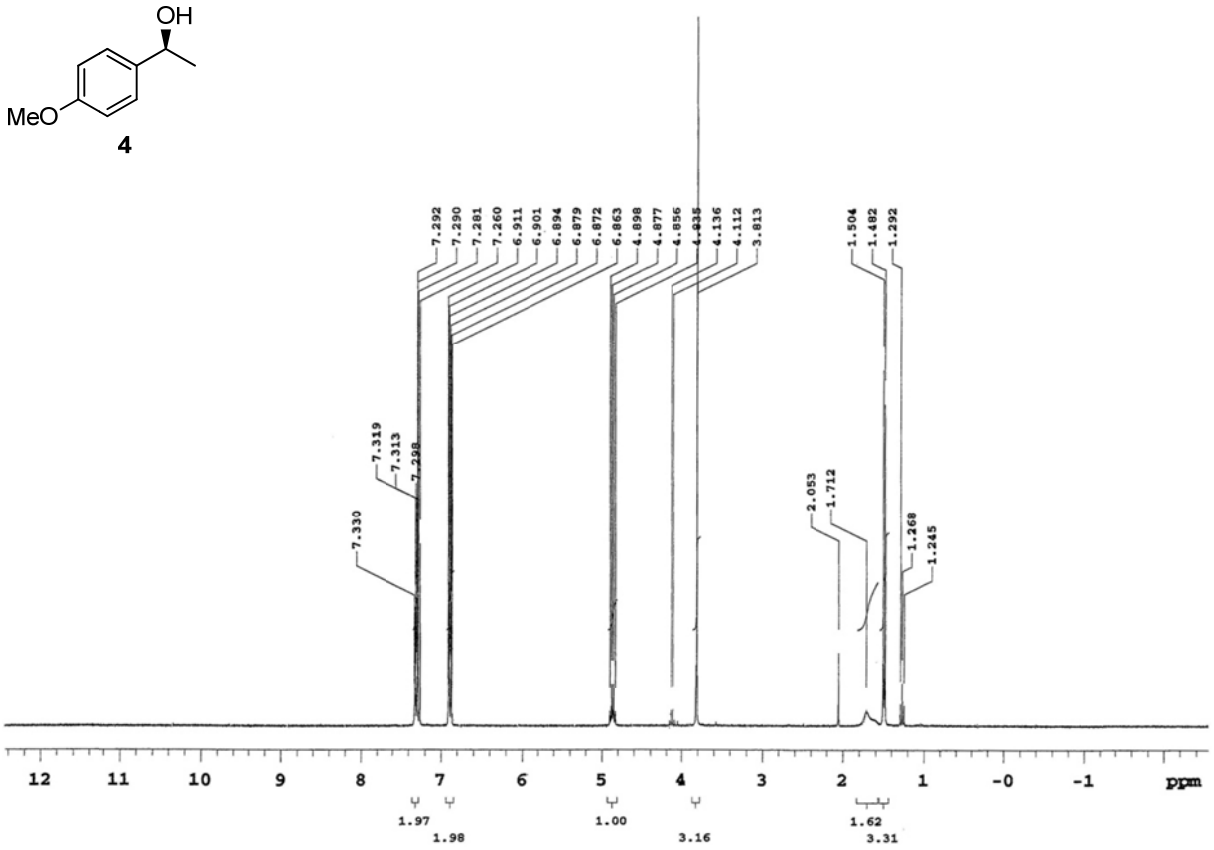


Fig. S12 ^{1}H NMR spectrum of **4**

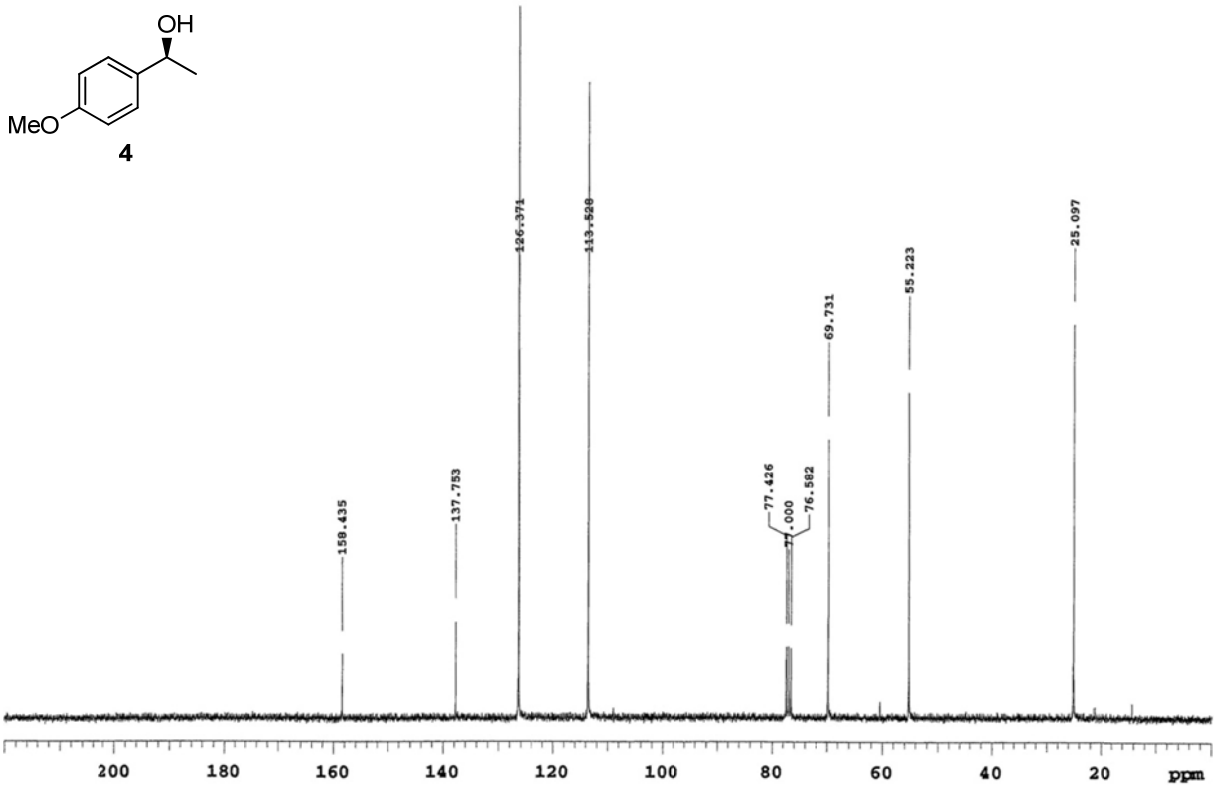


Fig. S13 ^{13}C NMR spectrum of **4**.

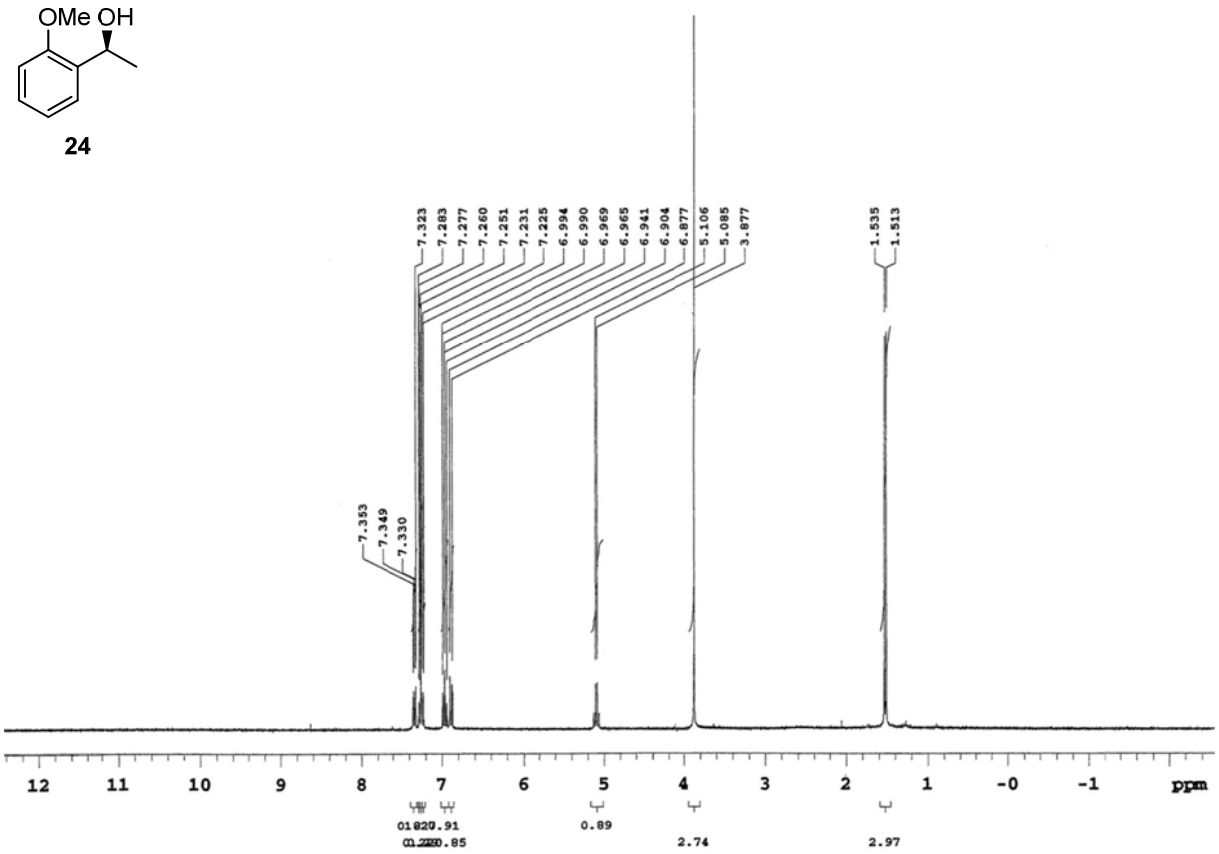


Fig. S14 ^{1}H NMR spectrum of **24**.

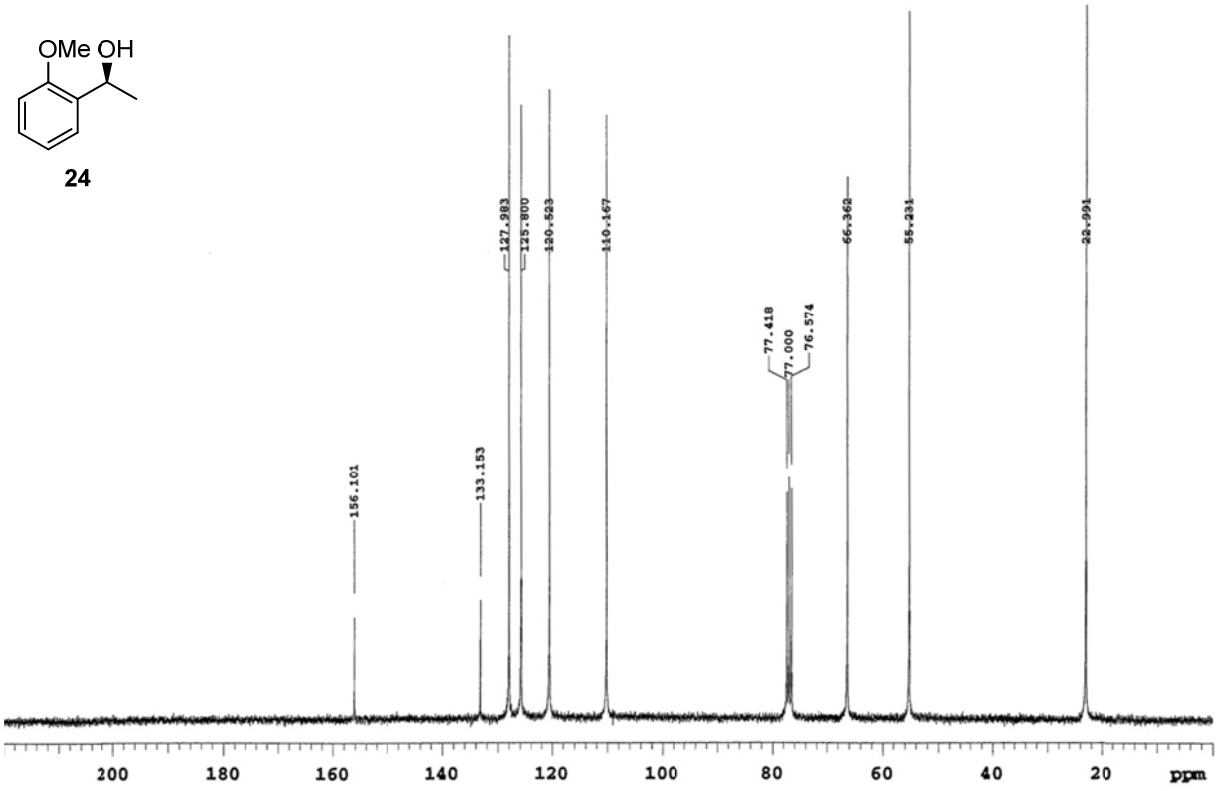


Fig. S15 ^{13}C NMR spectrum of **24**.

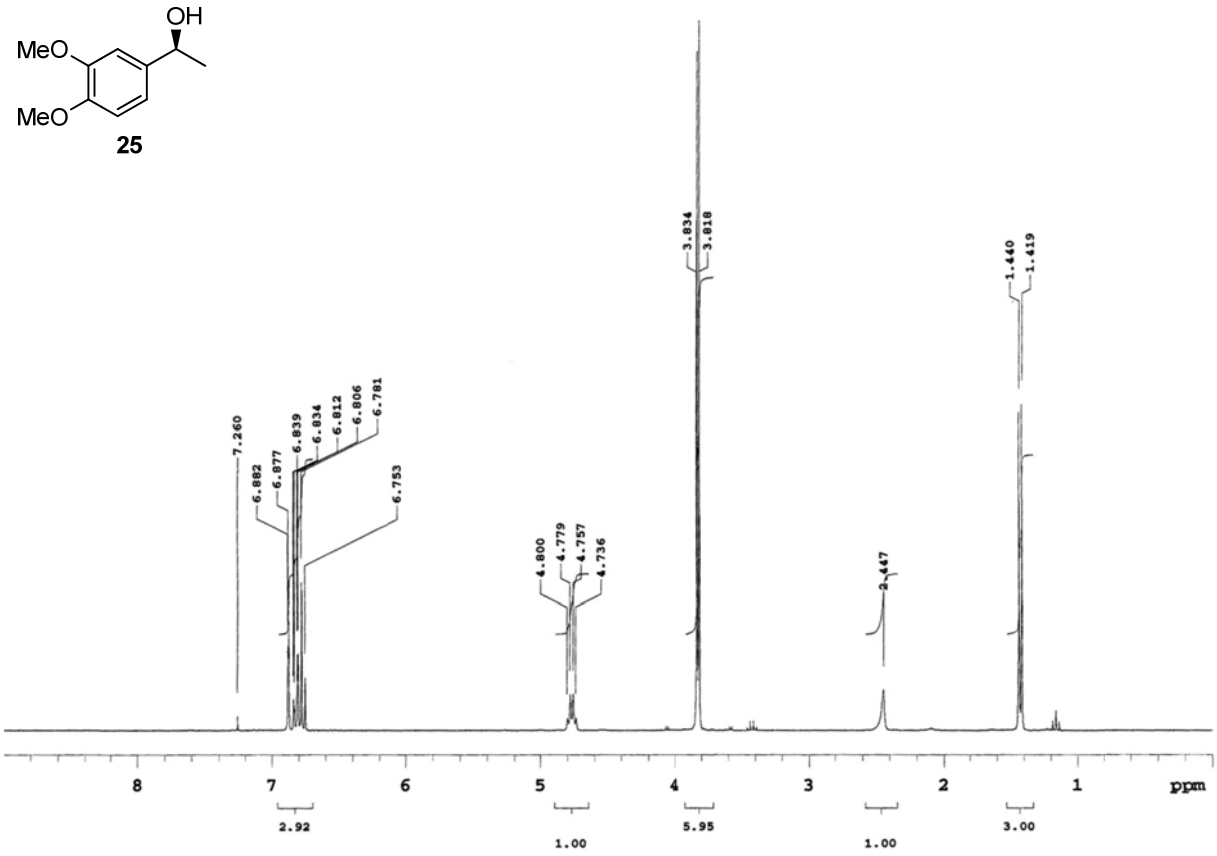


Fig. S16 ^{1}H NMR spectrum of **25**.

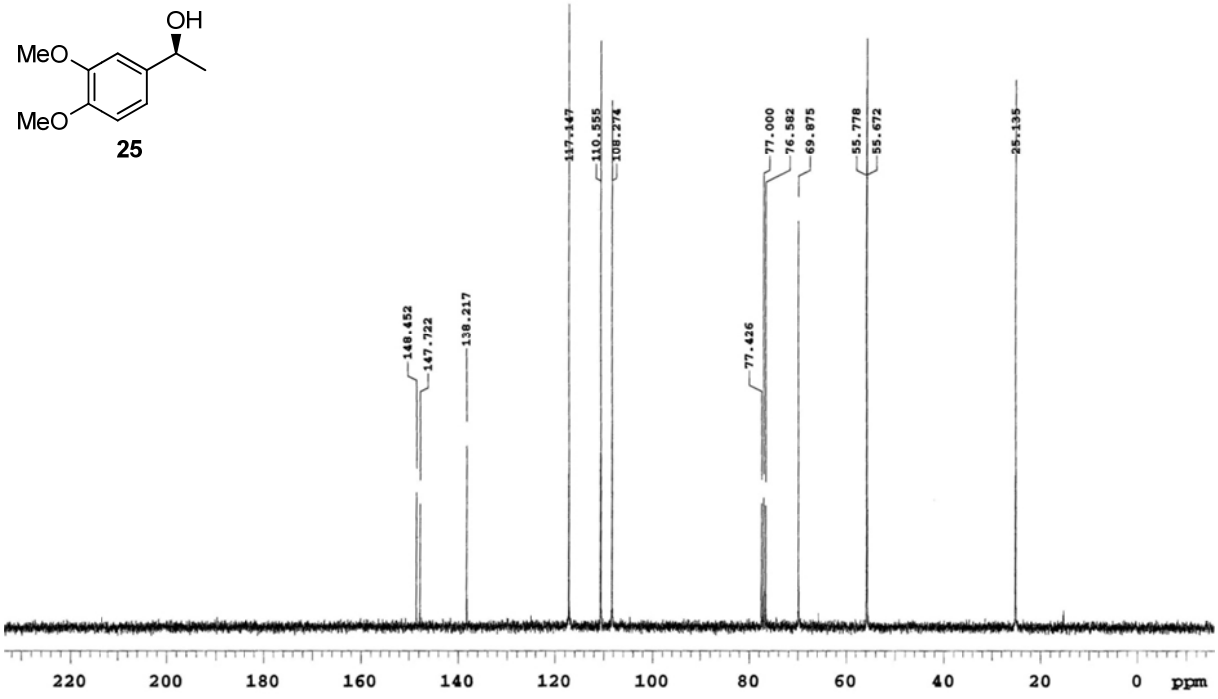


Fig. S17 ^{13}C NMR spectrum of **25**.

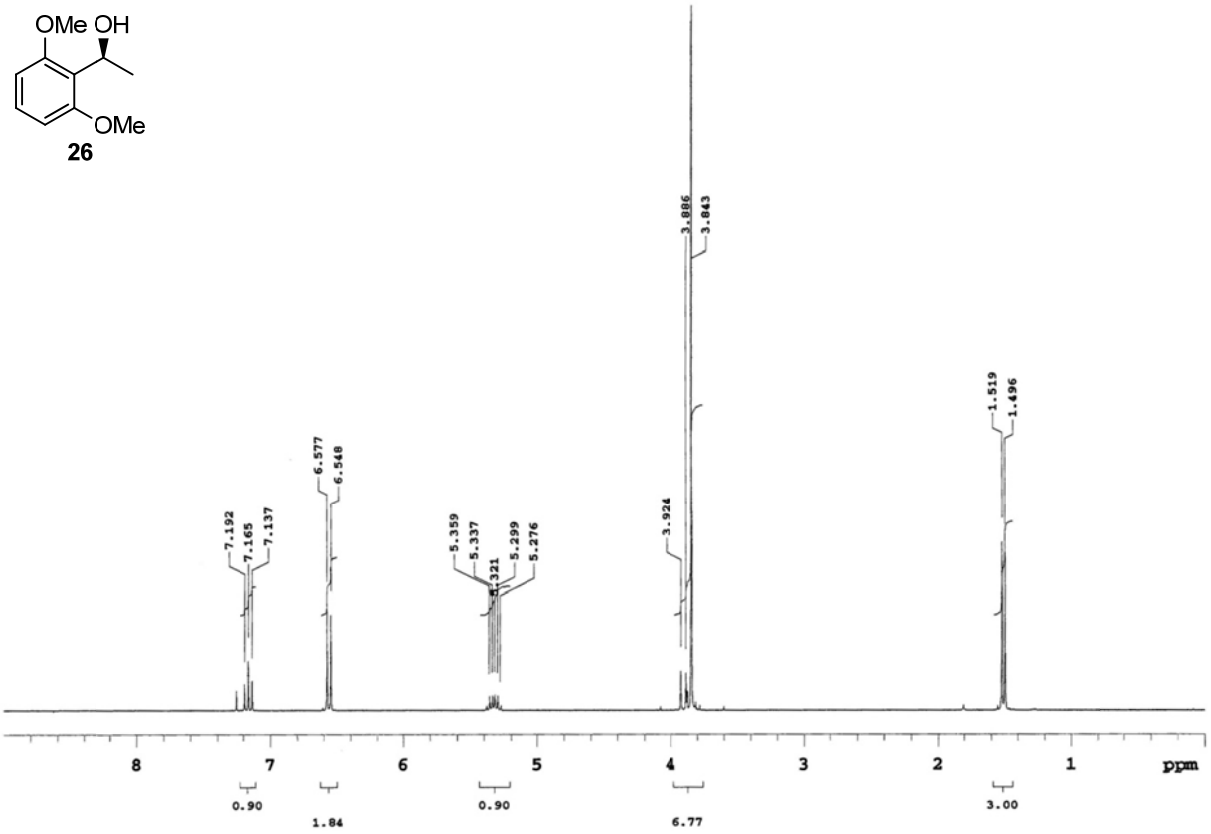


Fig. S18 ^{1}H NMR spectrum of **26**.

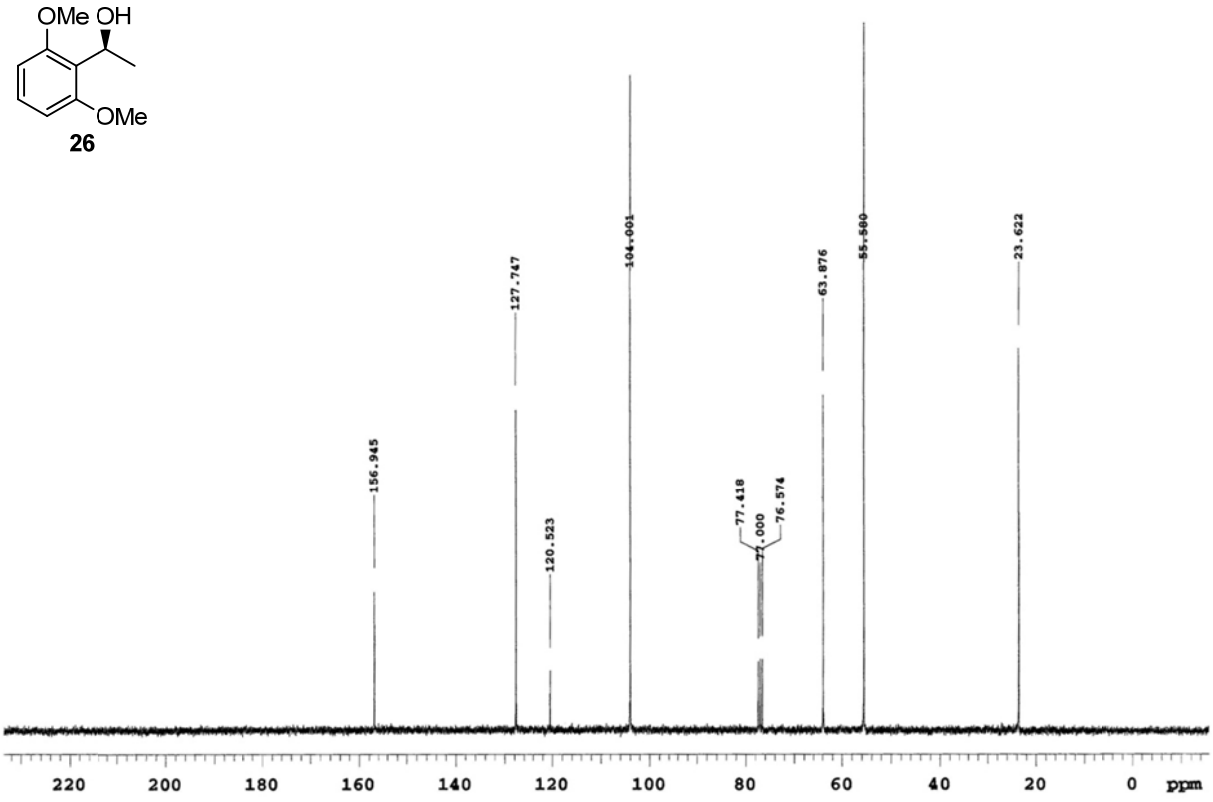


Fig. S19 ^{13}C NMR spectrum of **26**.

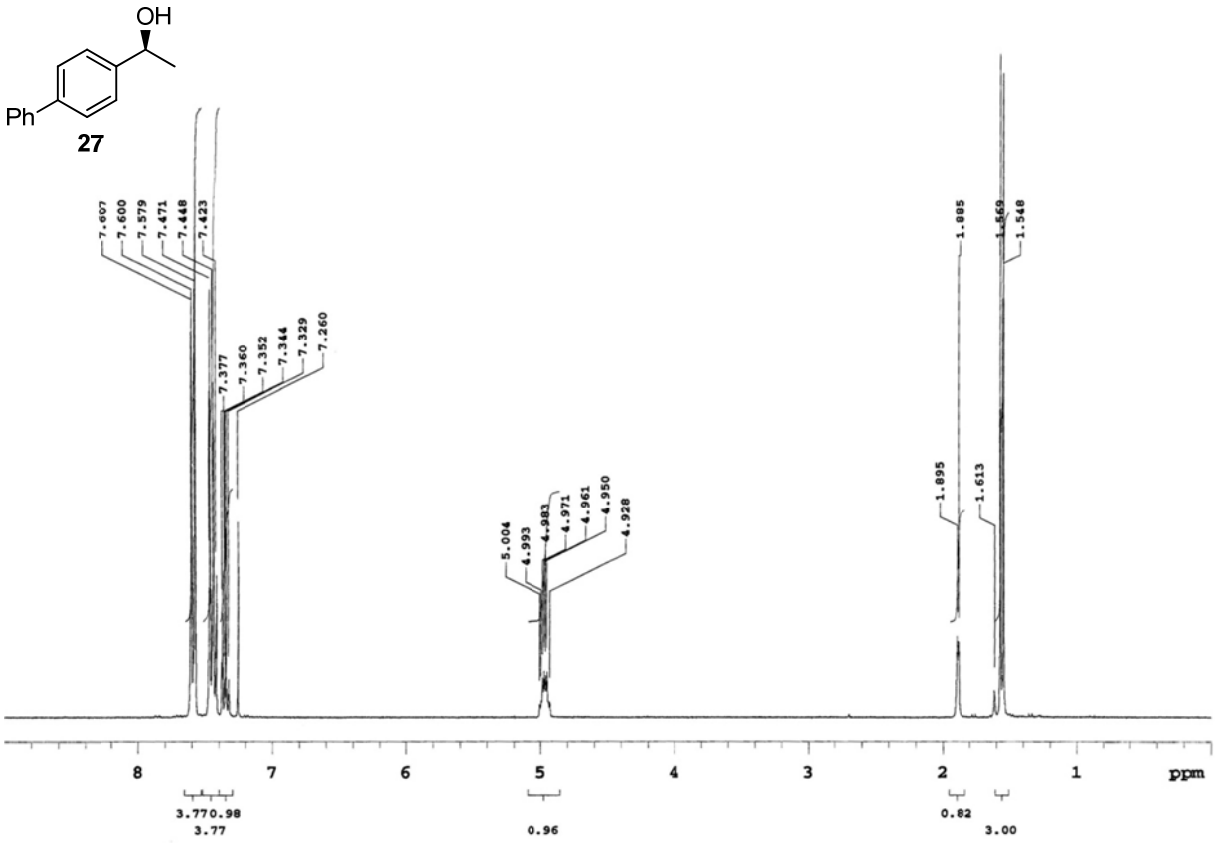


Fig. S20 ^{1}H NMR spectrum of **27**.

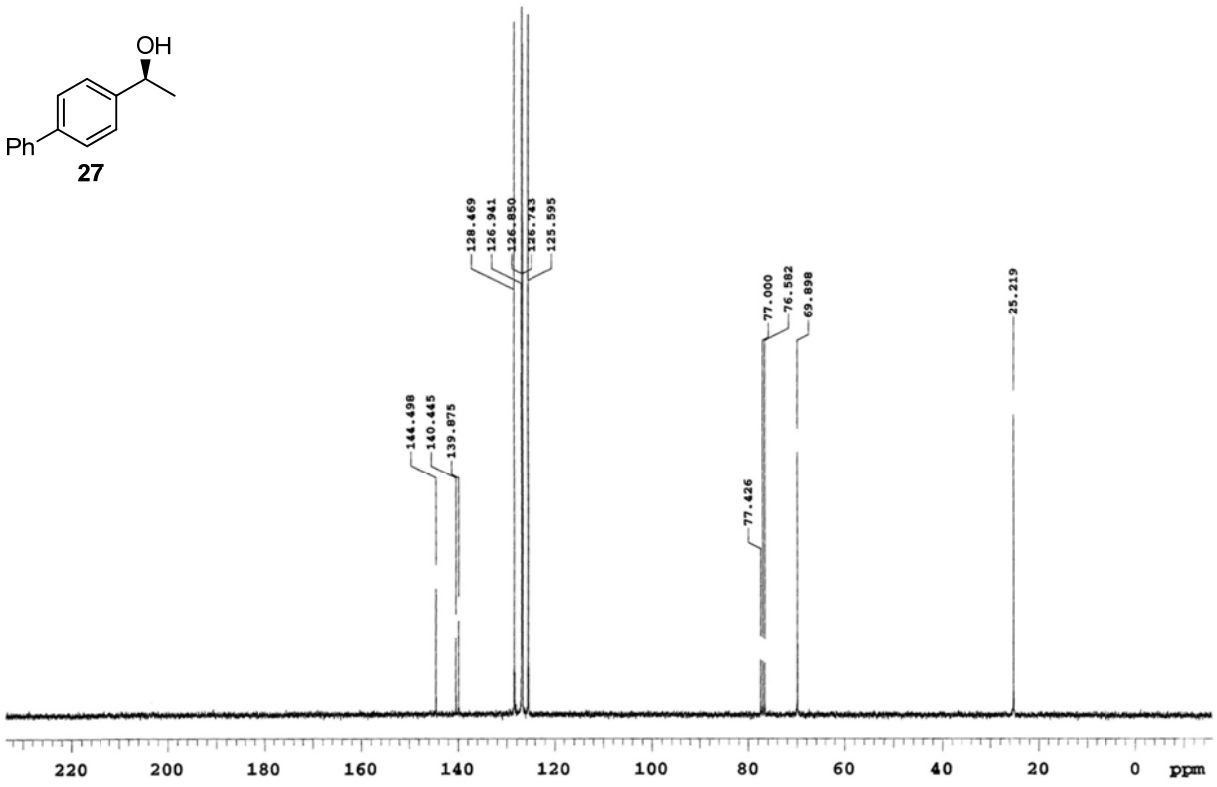


Fig. S21 ^{13}C NMR spectrum of **27**.

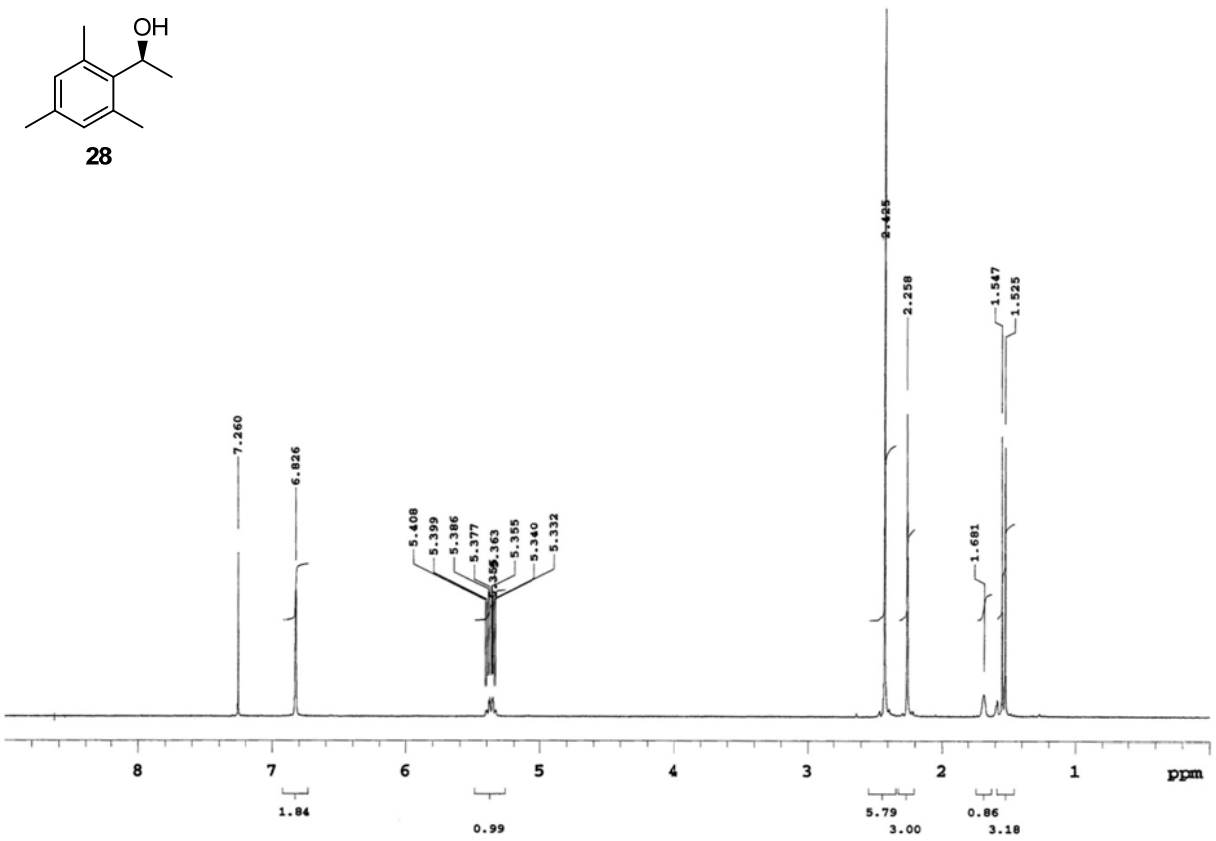


Fig. S22 ^{1}H NMR spectrum of **28**.

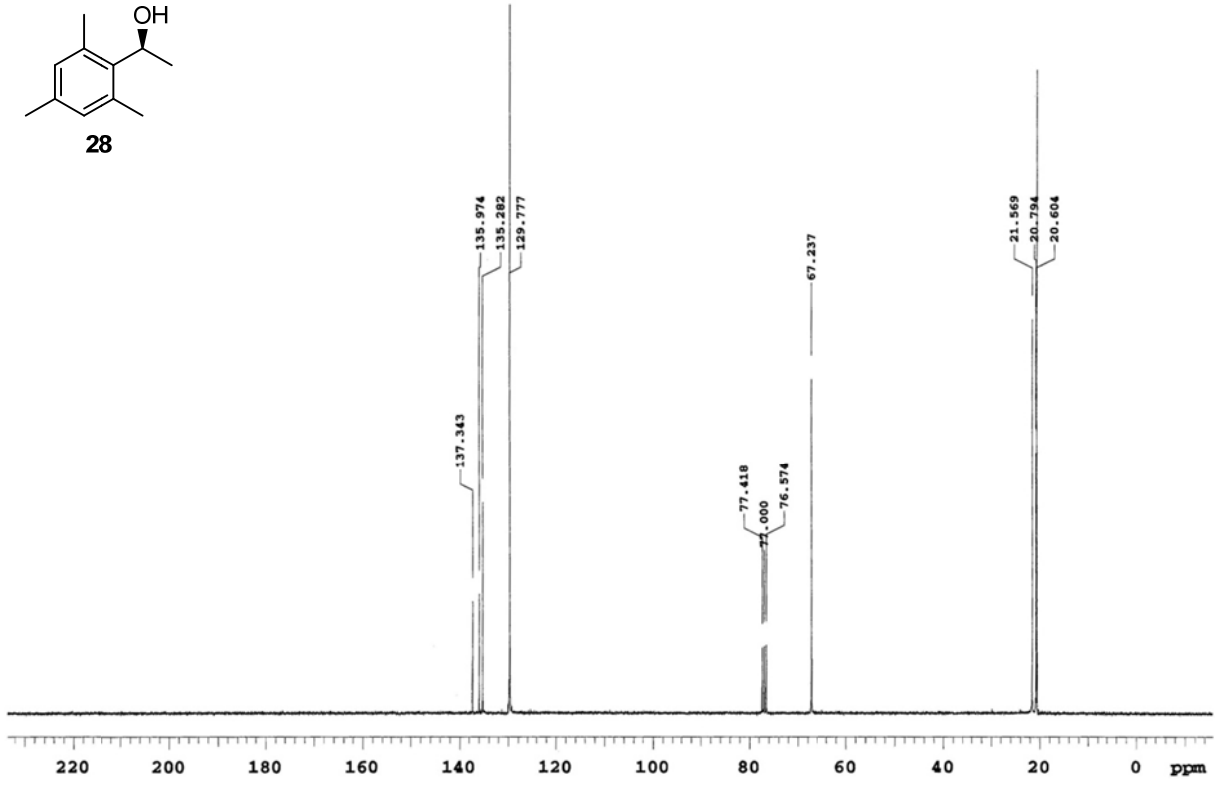


Fig. S23 ^{13}C NMR spectrum of **28**.

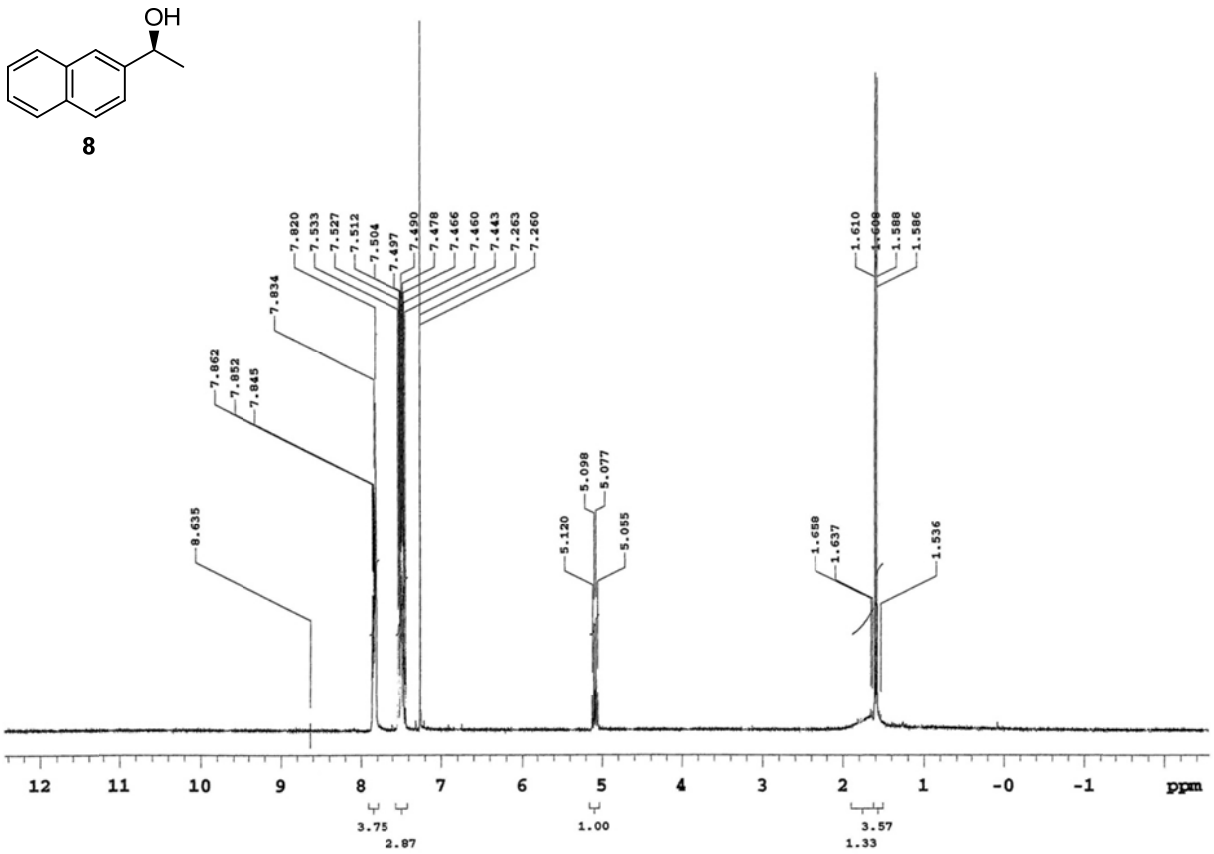


Fig. S24 ^{1}H NMR spectrum of **8**.

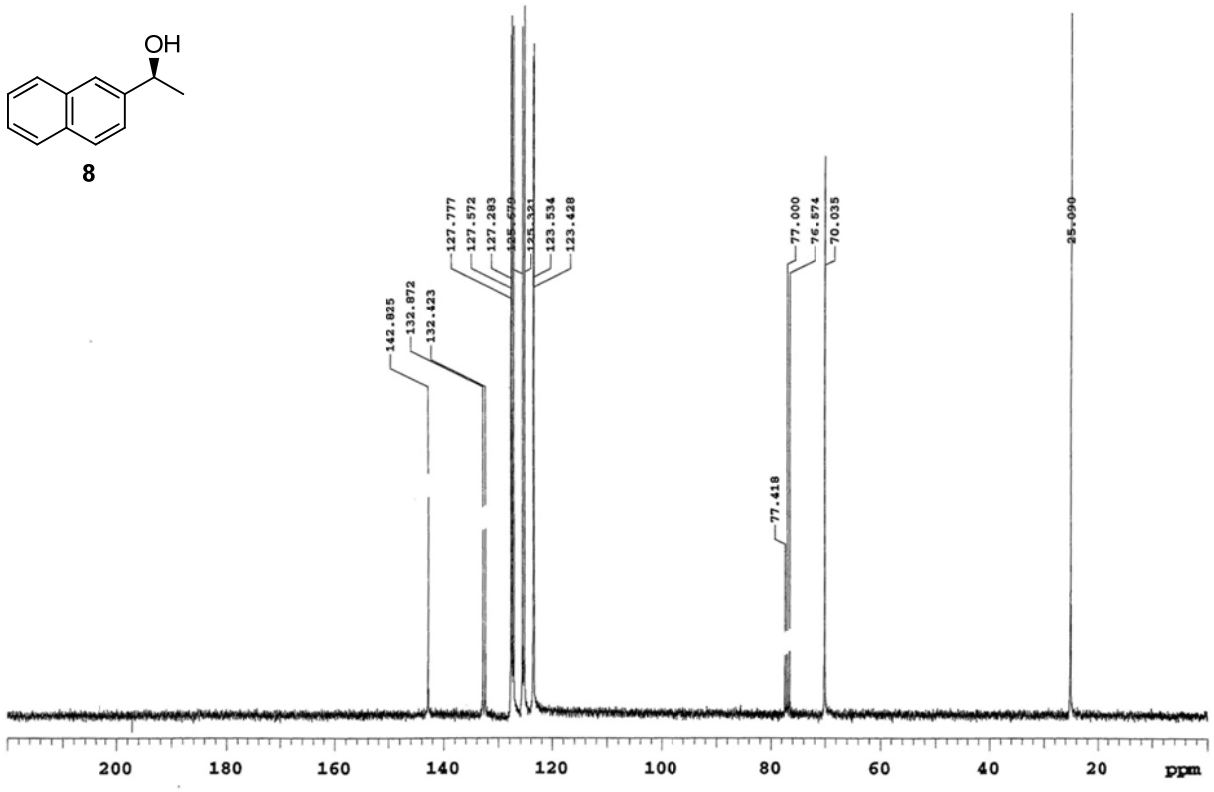


Fig. S25 ^{13}C NMR spectrum of **8**.

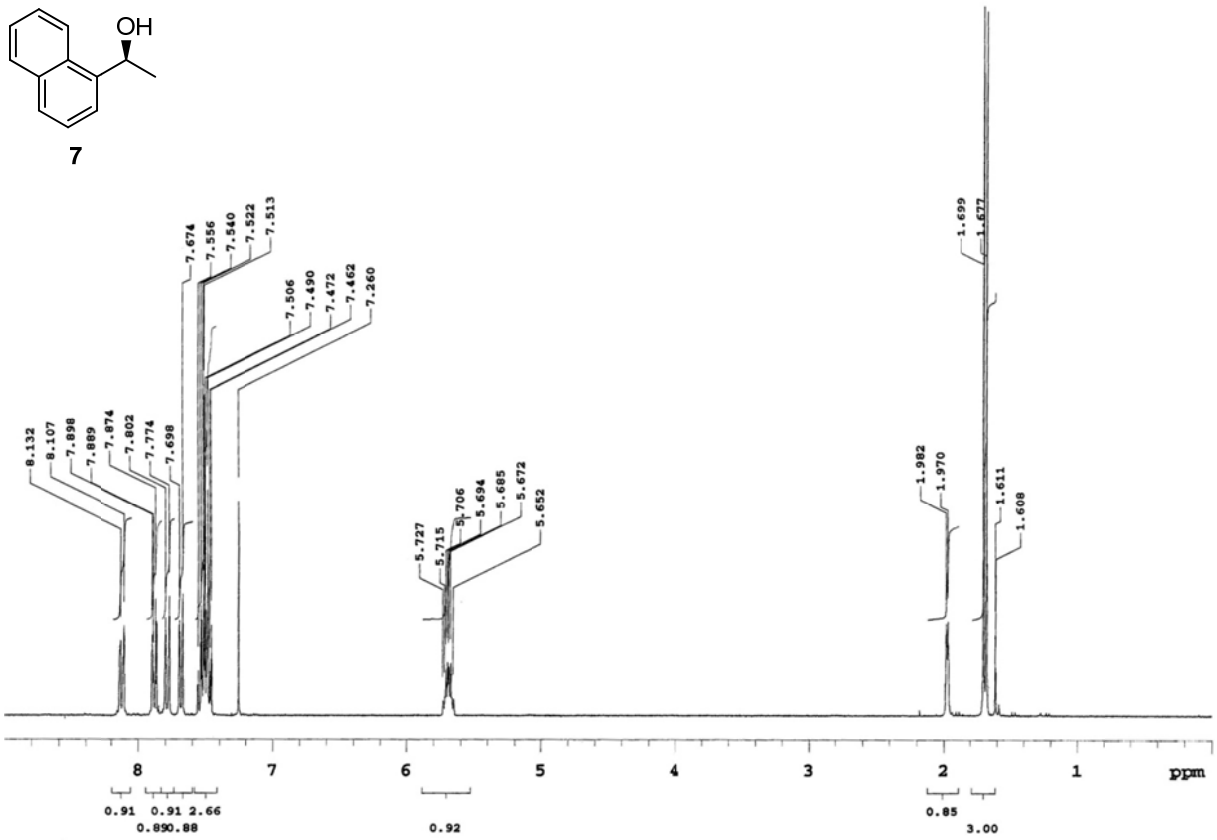


Fig. S26 ^{1}H NMR spectrum of **7**.

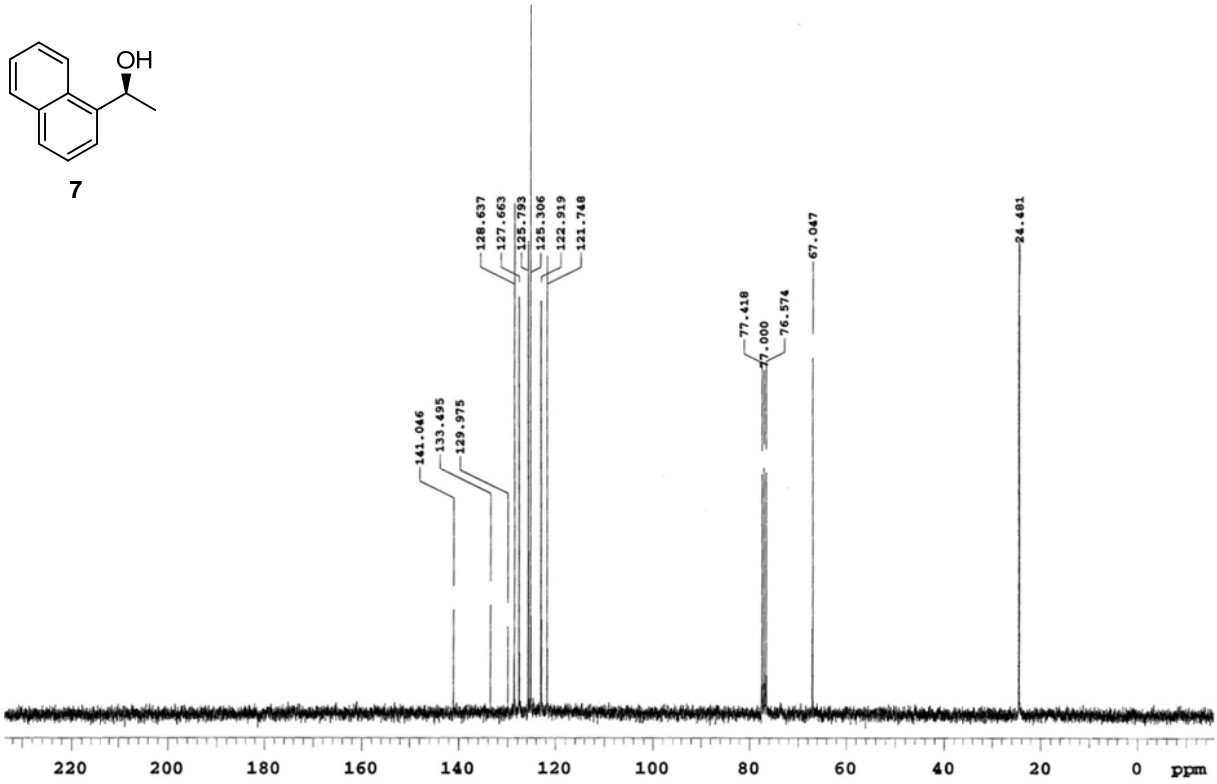


Fig. S27 ^{13}C NMR spectrum of **7**.

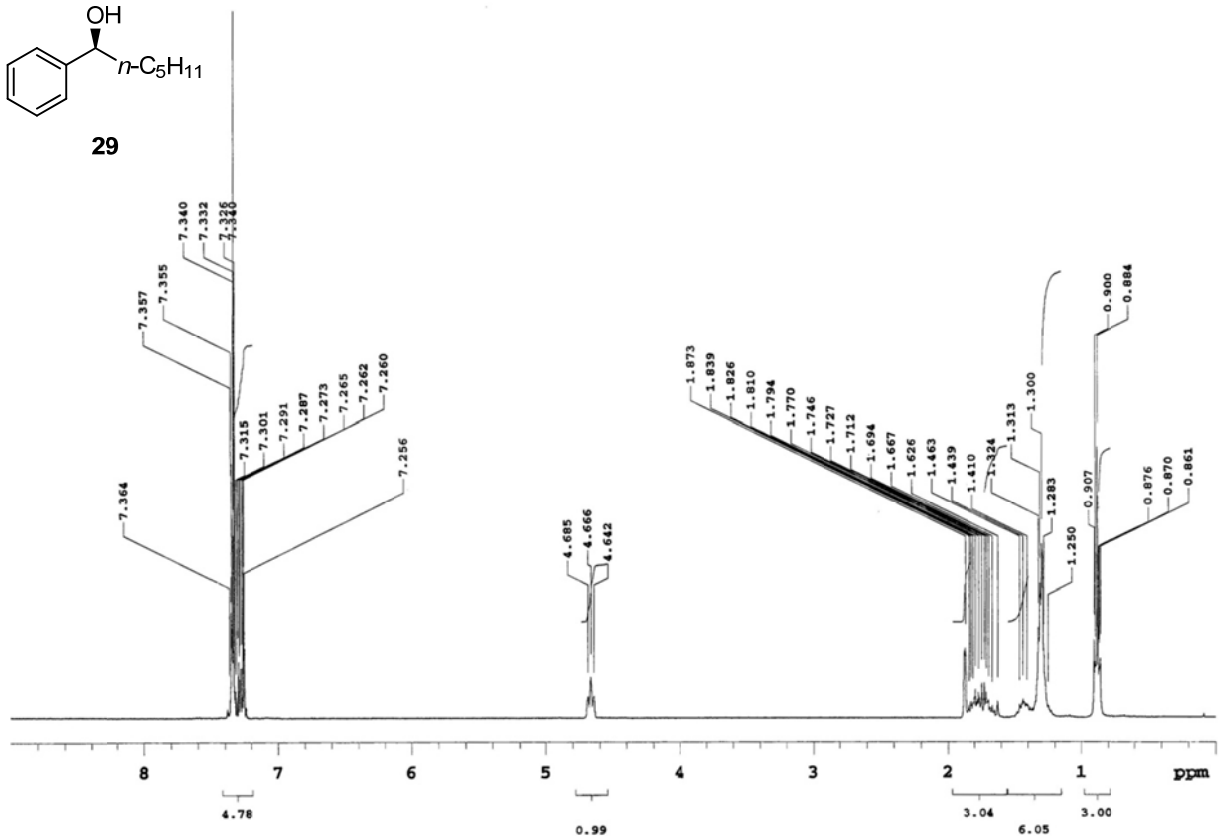


Fig. S28 ^{1}H NMR spectrum of **29**.

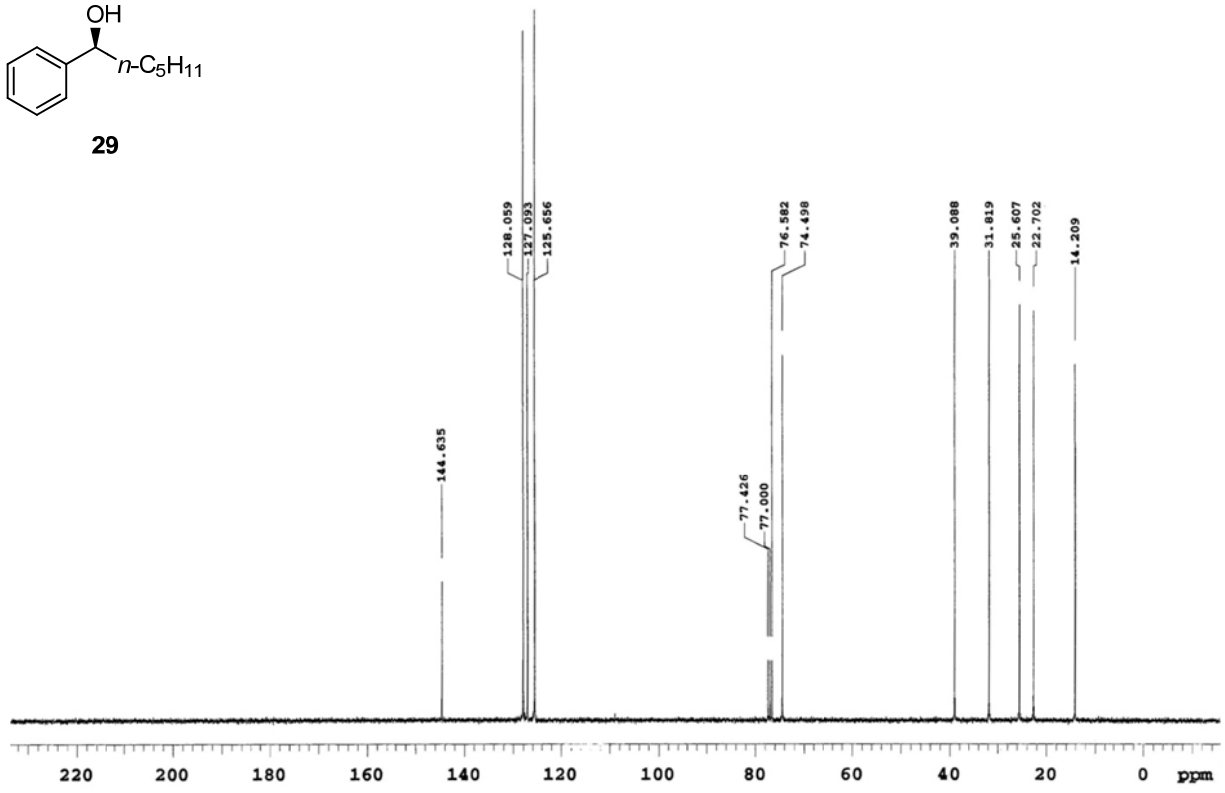


Fig. S29 ^{13}C NMR spectrum of **29**.

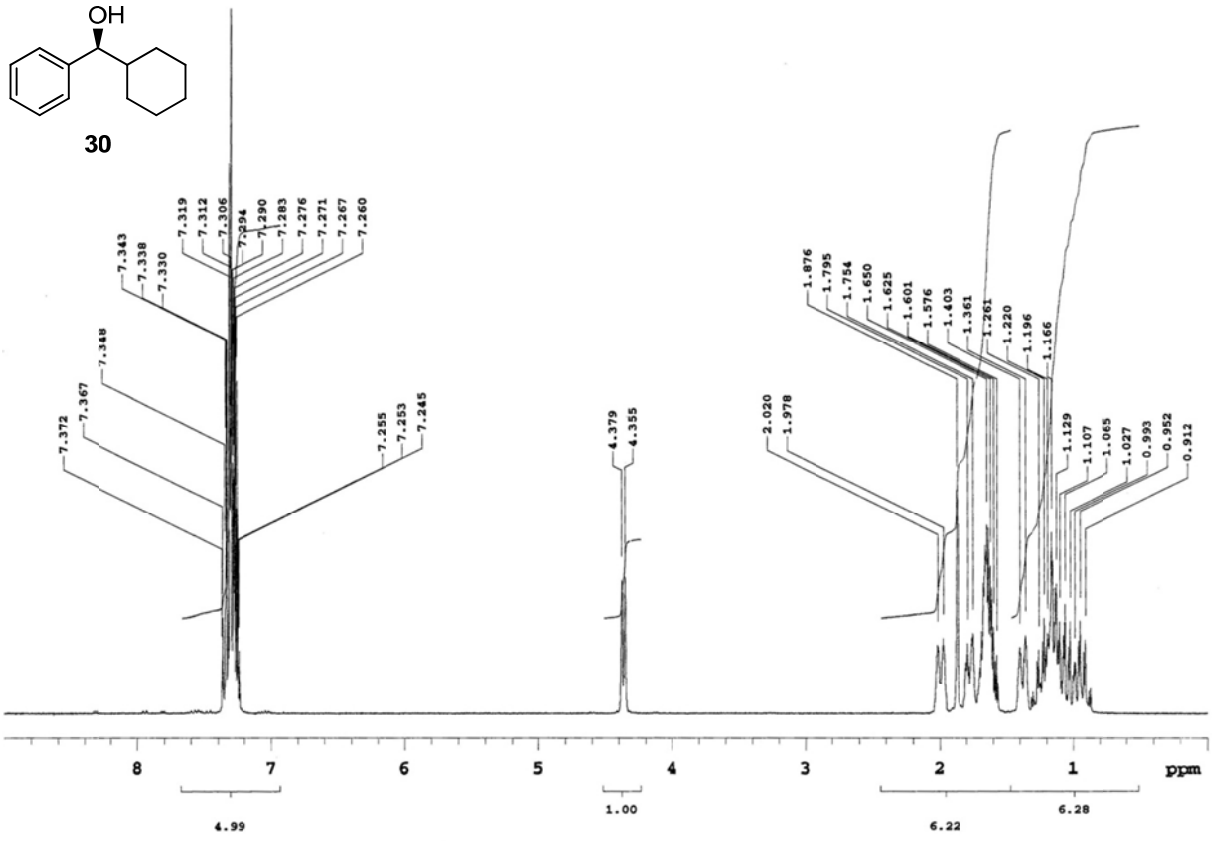


Fig. S30 ^{1}H NMR spectrum of **30**.

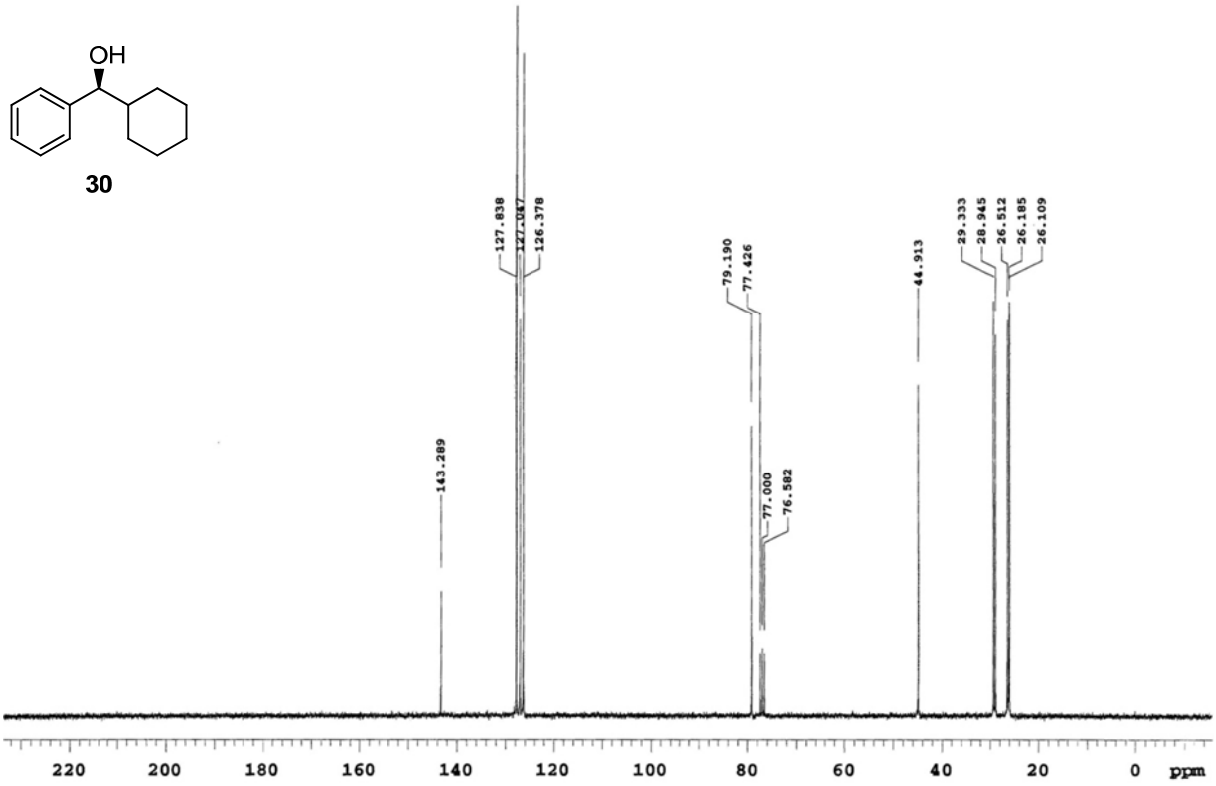


Fig. S31 ^{13}C NMR spectrum of **30**.

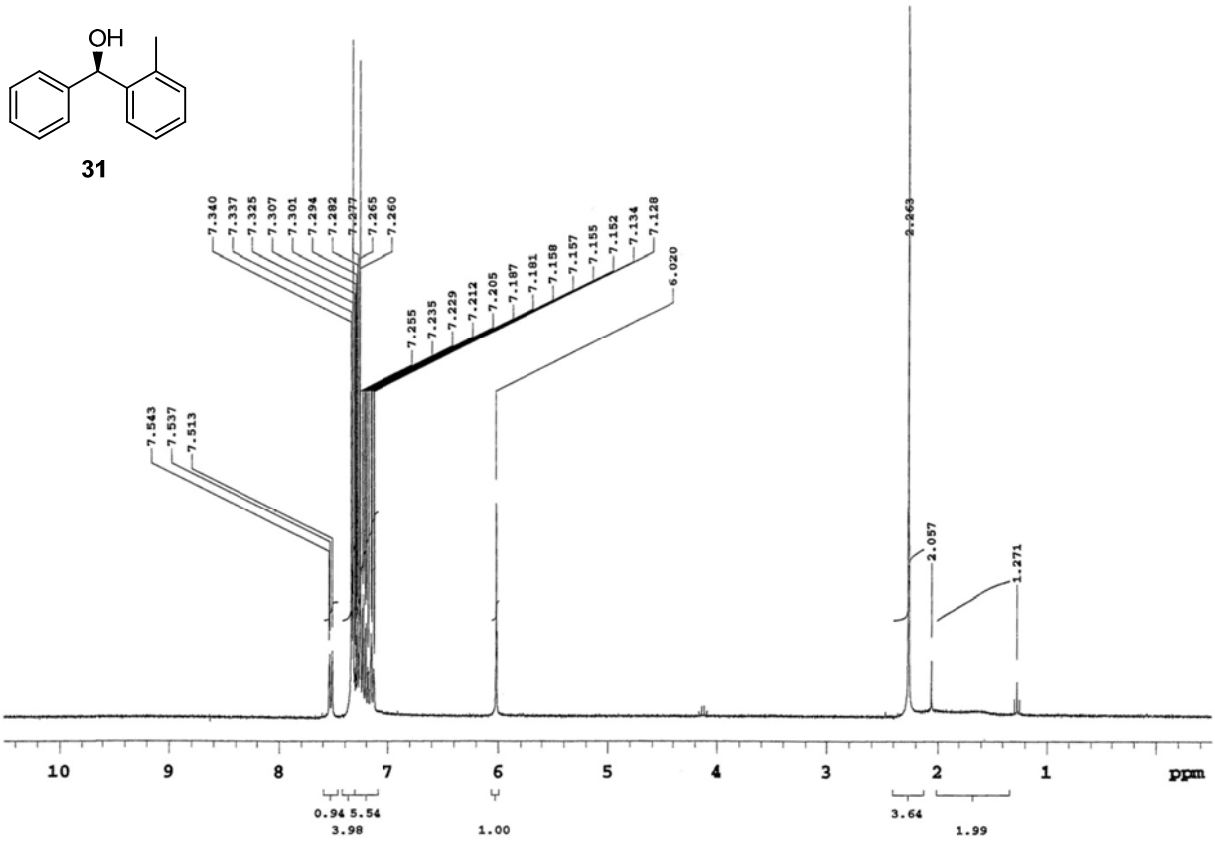


Fig. S32 ^{1}H NMR spectrum of **31**.

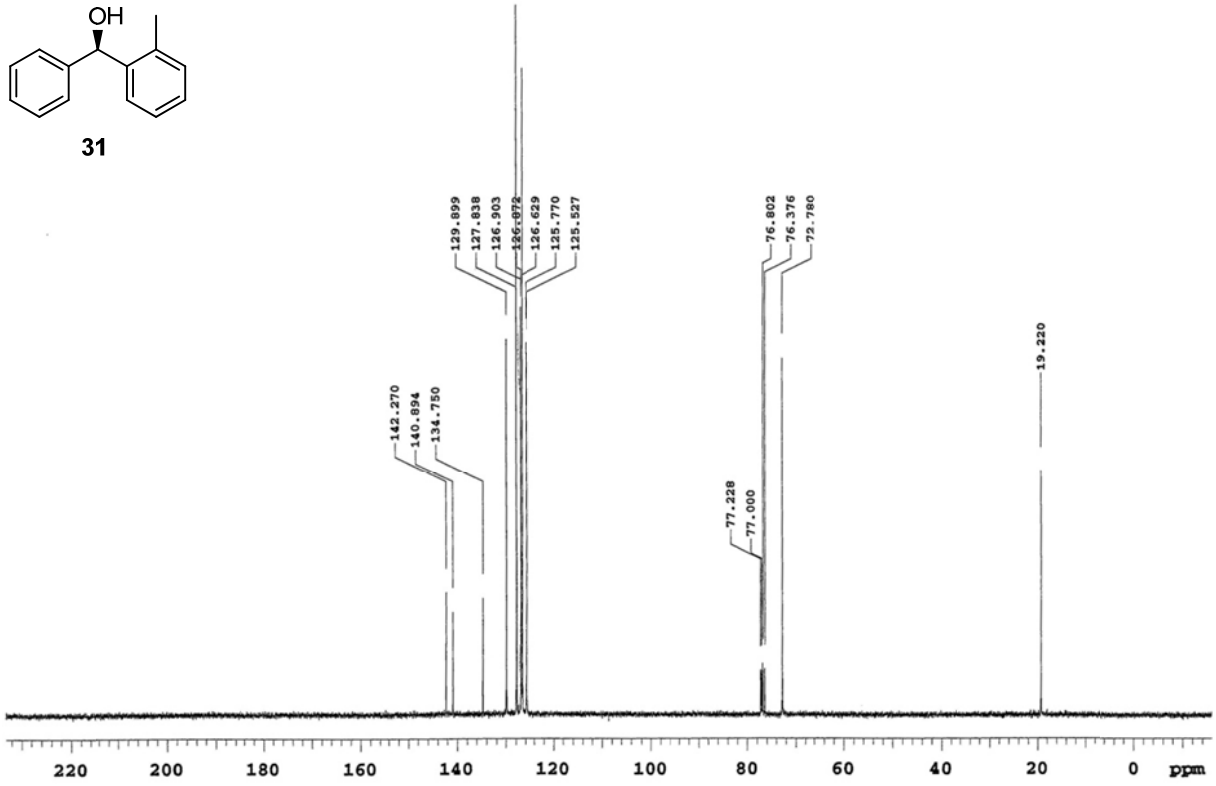
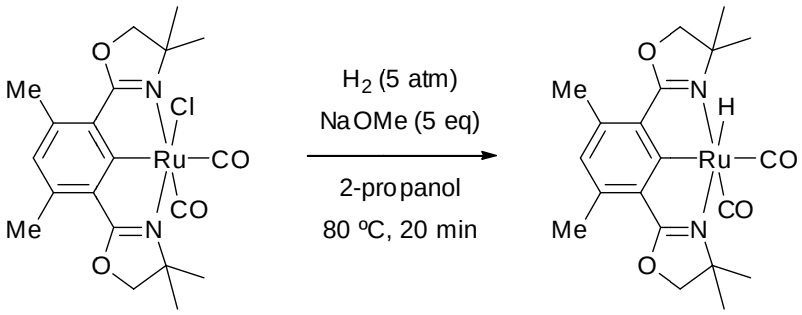


Fig. S33 ^{13}C NMR spectrum of **31**.

6. Reaction with H_2



22 **23**

A glass autoclave was charged with **22** (49.2 mg, 0.10 mmol) and NaOMe (27.4 mg, 0.51 mmol). After addition of 2-propanol (10 mL), the H_2 pressure was adjusted to 30 atm. The reaction mixture was stirred at 80 ºC for 20 min. The centrifugation of the mixture gave the yellowish solution. After removal of the solvent, the residue was washed with a small amount of hexane to give off-white solid of **23** (32.3 mg, 0.071 mmol, 71%).

^{1}H NMR (300 MHz, C_6D_6, rt): δ = –6.00 (s, 1H, Ru-*H*), 1.07 (s, 12H), 2.57 (d, *J* = 0.6 Hz, 6H), 3.65 (d, *J* = 8.3 Hz, 2H), 3.68 (d, *J* = 8.3 Hz, 2H), 3.61 (brs, 1H). ^{13}C NMR (75 MHz, C_6D_6, rt): δ = 19.3, 27.3, 27.8, 64.8, 80.1, 127.1, 128.5, 137.7, 169.7, 191.8, 205.5, 207.4.

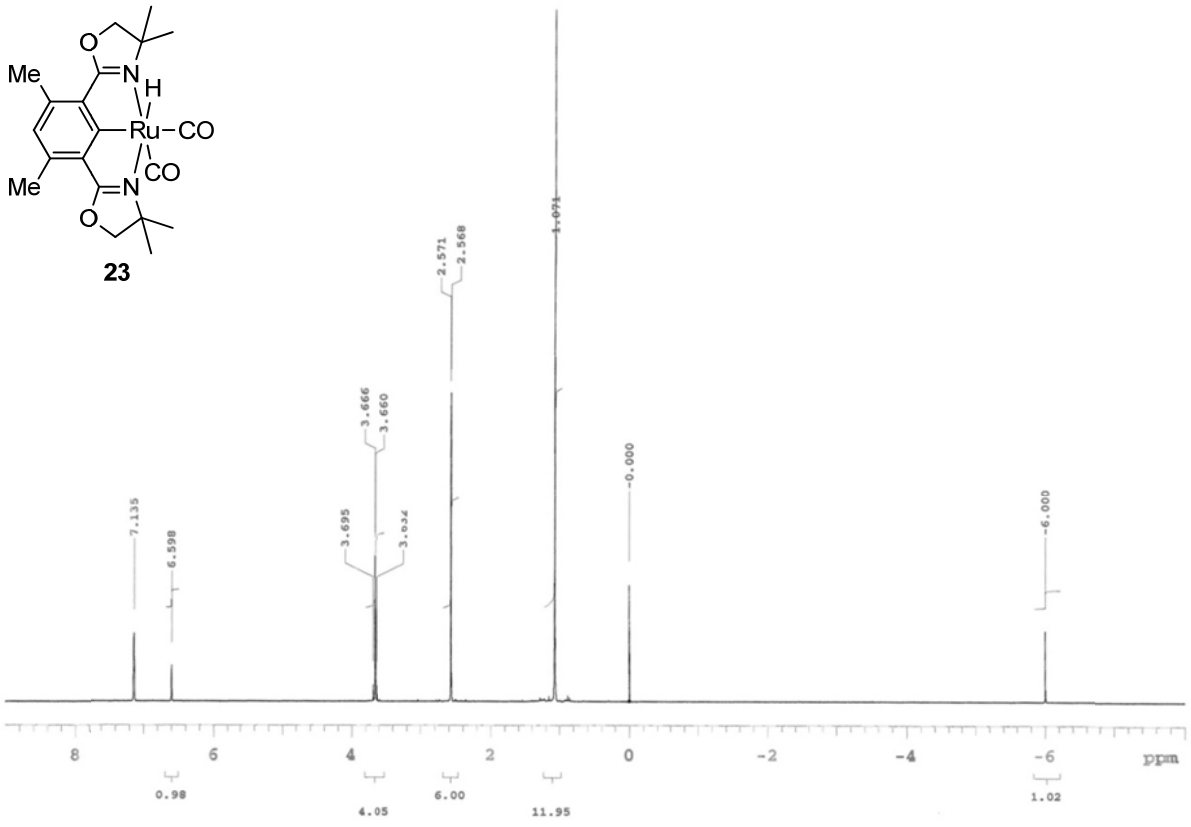


Fig S34 ^{1}H NMR spectrum of **23**

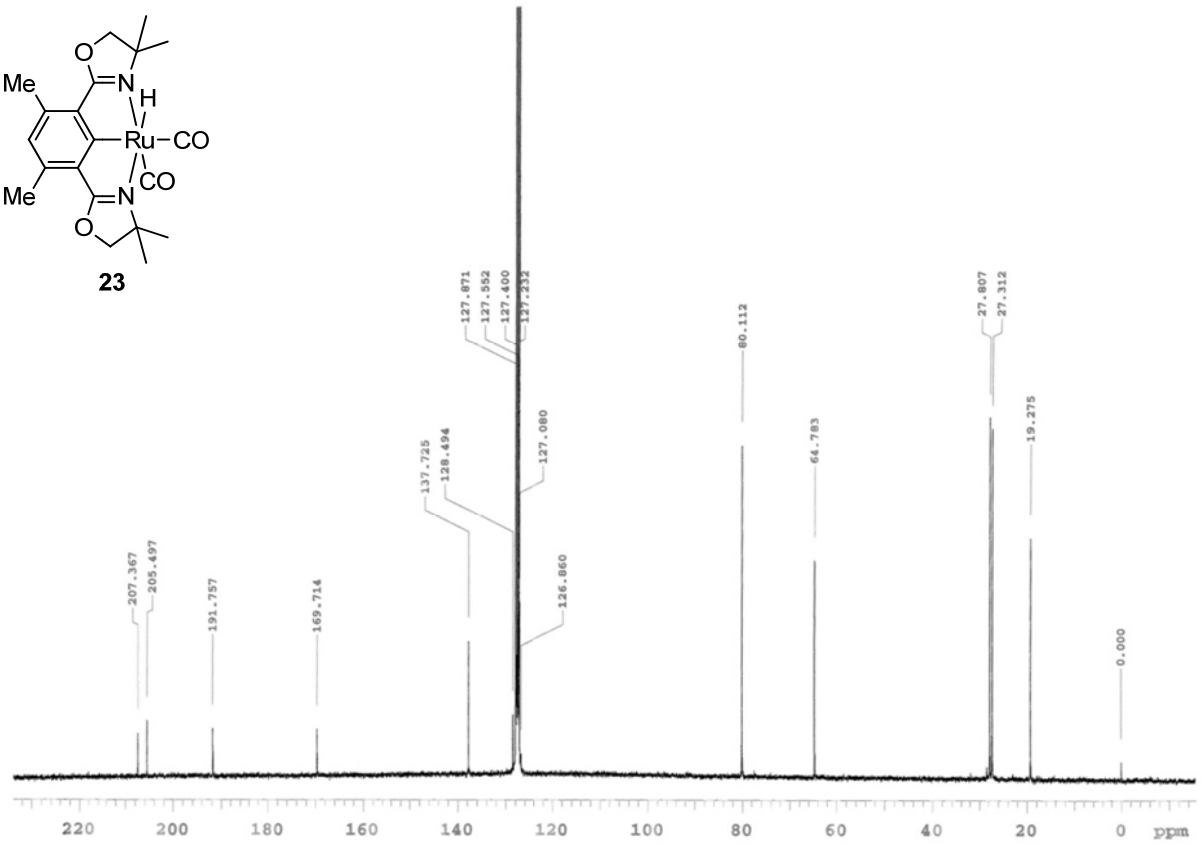


Fig S35 ^{13}C NMR spectrum of **23**

7. Time course experiments

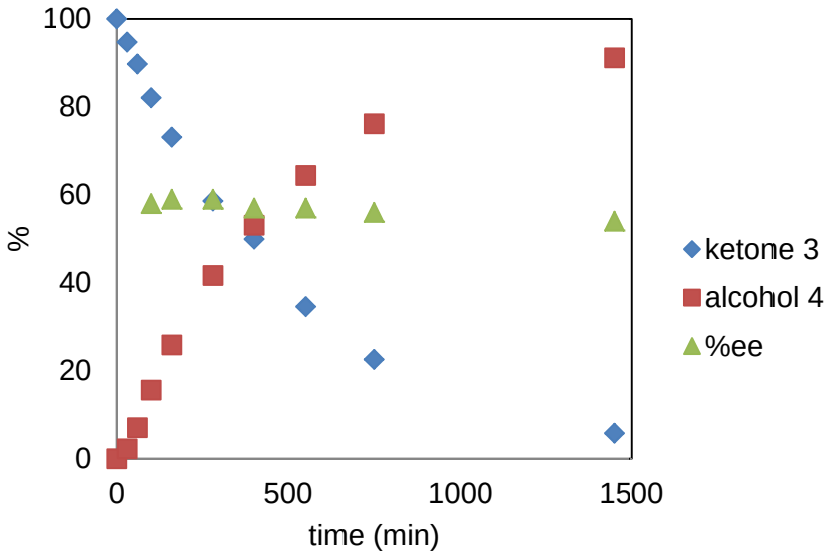


Fig S36 Reaction profile of the hydrogenation of **3** without the additive; Reaction condition: **3** (1.0×10^{-1} M), **1a** (1.0×10^{-3} M), NaOMe (2.0×10^{-2} M) 2-propanol, 40 °C, H_2 (30 atm).

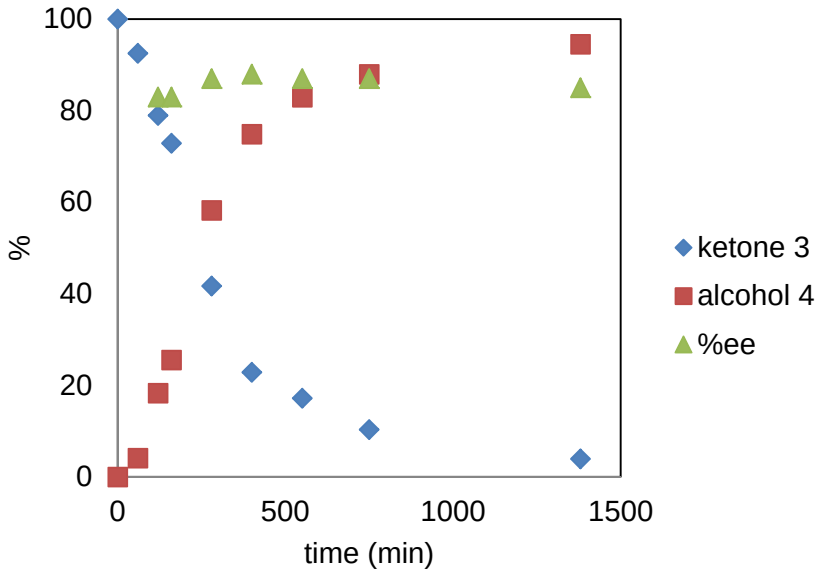


Fig S37 Reaction profile of the hydrogenation of **3** with the additive **5-(*S*)**; Reaction condition: **3** ($1.0x10^{-1}$ M), **1a** ($1.0x10^{-3}$ M), NaOMe ($2.0x10^{-2}$ M), **5-(*S*)** ($1.0x10^{-2}$ M), 2-propanol, 40 ºC, H_2 (30 atm).

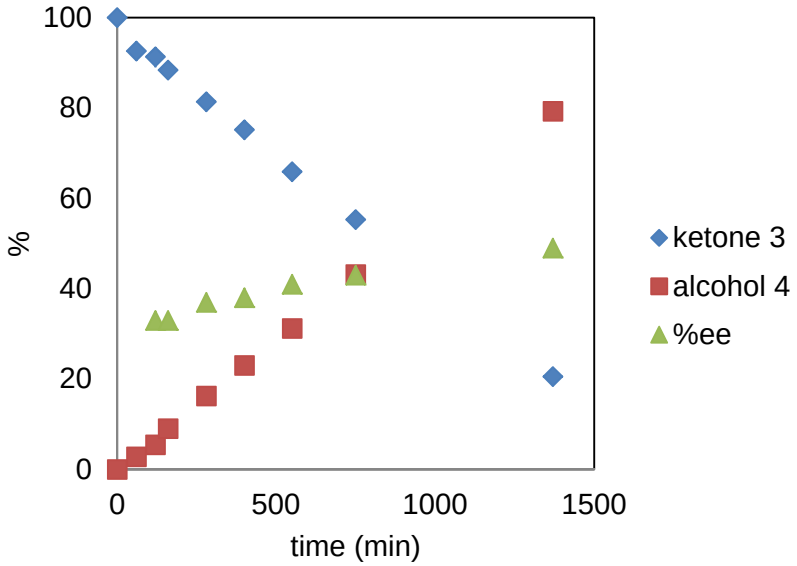


Fig S38 Reaction profile of the hydrogenation of **3** with the additive **5-(*R*)**; Reaction condition: **3** ($1.0x10^{-1}$ M), **1a** ($1.0x10^{-3}$ M), NaOMe ($2.0x10^{-2}$ M), **5-(*R*)** ($1.0x10^{-2}$ M), 2-propanol, 40 ºC, H_2 (30 atm).

8. References

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