Supplementary Information

A one-pot two-step synthesis of tertiary alcohols combining the biocatalytic laccase/TEMPO oxidation system with organolithium reagents in aerobic aqueous media at room temperature

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1.- General Methods

All reagents were obtained from commercial suppliers and used without further purification. Alcohols **1a-f** were purchased from commercial source. Laccase from *Trametes versicolor* or *Rhus Vernicifera* and TEMPO were purchased from Sigma Aldrich. Organolithium and organomagnesium reagents were purchased from Sigma Aldrich: *i*) 2.5 M solution of *n*-BuLi in hexanes; *ii*) 1.6 M solution of MeLi in Et_2O; *iii*) 1.4 M solution of *s*-BuLi in cyclohexane; *iv*) 1.7 M solution of *t*-BuLi in pentane; *iv*) 1.9 M solution of PhLi in dibutyl ether; and *v*) 1.0 M solution of PhMgBr in THF. Concentrations of all organolithium reagents were checked by titration with *L*-menthol,[1] and for the Grignard reagent, titrating against iodine was employed.[2] All the rest of reagents and solvents were of the highest quality available.

NMR spectra ($CDCl_3$) were obtained using a Bruker DPX-300 (^1H, 300.13 MHz; $^{13}C\{^1H\}$, 75.4 MHz) spectrometer and employing the δ scale (ppm) for chemical shifts. Calibration was made on the signal of the solvent (^1H: $CDCl_3$, 7.26 ppm; ^{13}C: $CDCl_3$, 77.0 ppm). Gas chromatography (GC) analyses were performed on an Agilent Technologies 7820A chromatograph equipped with a HP-5 (30 m x 0.32 mm x 0.25 μm) column.

Spectroscopic data of ketones **2a-f**[3,4] and tertiary alcohols **3a**,[4] **3b**,[4] **3c**,[4] **3d**,[5] **3e**,[4] **3f**,[6] **3h**,[7] **3i**[7] are in agreement with those reported in the literature.

2.- Protocols

General Procedure for oxidation of secondary alcohols 1a-f into ketones 2a-f promoted by the system laccase/TEMPO in water

T. versicolor laccase (14 mg, 10 U/mg) and TEMPO (12 mg, 10 mol%) were added to a 0.73 mmol (0.1 mL) of the secondary alcohol **1a** in water (1 mL) and the mixture was stirred vigorously in an open-to-air vial at room temperature for 24 h (the oxidation reaction was monitored by GC analysis). Then, the reaction mixture was extracted with ethyl acetate (3 x 5 mL), the organic layers were combined, washed, dried with $MgSO_4$ and the solvents evaporated under vacuum. The identity of the resulting ketone **1a** was confirmed by ^{1}H-RMN analysis of the crude product after comparison with reported spectra.[3]

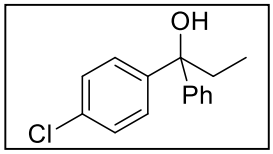
Procedure for direct conversion of 1-phenylpropan-1-ol (1a) into tertiary alcohols 3a-e through one-pot combination of the laccase/TEMPO oxidation system with the chemoselective addition of RLi/RMgX in biphasic aqueous media, at room temperature and in the presence of air

T. versicolor laccase (7 mg, 10 U/mg) and TEMPO (6 mg, 10 mol%) were added to 0.365 mmol (0.05 mL) of the secondary alcohol **1a** in water (0.5 mL) and the mixture was stirred vigorously in an open-to-air vial at room temperature for 24 h (the oxidation reaction was monitored by GC analysis). Once the oxidation reaction was completed (GC analysis, 24 h), 0.5 mL of CPME were added to form a biphasic reaction medium. Next, 3 equivalents of the corresponding organolithium (RLi) or Grignard (RMgX) reagents were added to the reaction mixture at room temperature, under air. After 3 s, 2.5 mL of saturated aqueous solution of NH_4Cl were added, and the mixture was extracted with ethyl acetate (3 x 5 mL). The combined organic phases were washed, dried over anhydrous $MgSO_4$, and the solvent was concentrated *in vacuo*.

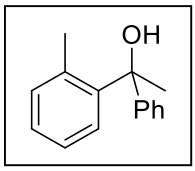
Procedure for direct conversion of secondary alcohols 1a-f into tertiary alcohols 3e-j through one-pot combination of the laccase/TEMPO oxidation system with the chemoselective addition of PhLi in biphasic aqueous media, at room temperature and in the presence of air

T. versicolor laccase (7 mg, 10 U/mg) and TEMPO (6 mg, 10 mol%) were added to a 0.365 mmol of the desired secondary alcohol **1a-f** in water (0.5 mL) and the mixture was stirred vigorously in an open-to-air vial at room temperature for 24 h (the oxidation reaction was monitored by GC analysis). Once the oxidation reaction was completed (GC analysis, 24 h), 0.5 mL of CPME were added to form a biphasic reaction medium. Next, 3 equivalents of the PhLi (0.58 mL) were added to the reaction mixture at room temperature, under air. After 3 s, 2.5 mL of saturated aqueous solution of NH_4Cl were added, and the mixture was extracted with ethyl acetate (3 x 5 mL). The combined organic phases were washed, dried over anhydrous $MgSO_4$, and the solvent was concentrated *in vacuo*.

3.- Characterization of new compounds 3g and 3j



1-(4-chlorophenyl)-1-phenylpropan-1-ol (3g): yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.2, 3H), 2.08 (s, OH), 2.33 (q, *J* = 7.2, 2H), 7.26-7.44 (m, 9H); $^{13}C\{^{1}H\}$ NMR (300 MHz, $CDCl_3$) δ 8.1, 34.4, 78.2, 126.0, 127.1, 127.6, 128.2, 128.3 132.6, 145.4, 146.5; FT-IR (film, cm^{-1}): 3510 (ν_{OH}); 3060, 3031 (aromatic ν_{CH}); 2975, 2937, 2876 (ν_{CH} sp^3); 1685, 1587, 1570 (aromatic $\nu_{C=C}$); 1087 (ν_{C-OH}); 800 (aromatic δ_{CH} *para*-substitution); 738, 701 (aromatic δ_{CH} *mono*-substitution).



1-phenyl-1-(o-tolyl)ethan-1-ol (3j): yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.96 (s, 3H), 2.02 (s, 3H), 2.15 (s, OH), 7.12-7.15 (m, 1H), 7.23-7.35 (m, 7H), 7.71-7.74 (m, 1H); $^{13}C\{^{1}H\}$ NMR (300 MHz, $CDCl_3$) δ 21.4, 32.2, 76.8, 125.3, 125.4, 126.0, 126.6, 127.7, 128.1, 132.5, 137.2, 144.6, 148.0; FT-IR (film, cm^{-1}): 3445 (ν_{OH}); 3059, 3024 (aromatic ν_{CH}); 2973, 2927 (ν_{CH} sp^3); 1601, 1486, 1447 (aromatic $\nu_{C=C}$); 757 (aromatic δ_{CH} *ortho*-disubstitution); 728, 701 (aromatic δ_{CH} *mono*-substitution).

4.- NMR spectra data

^{1}H and ^{13}C NMR spectra of 3-phenyl-heptan-3-ol (3a)

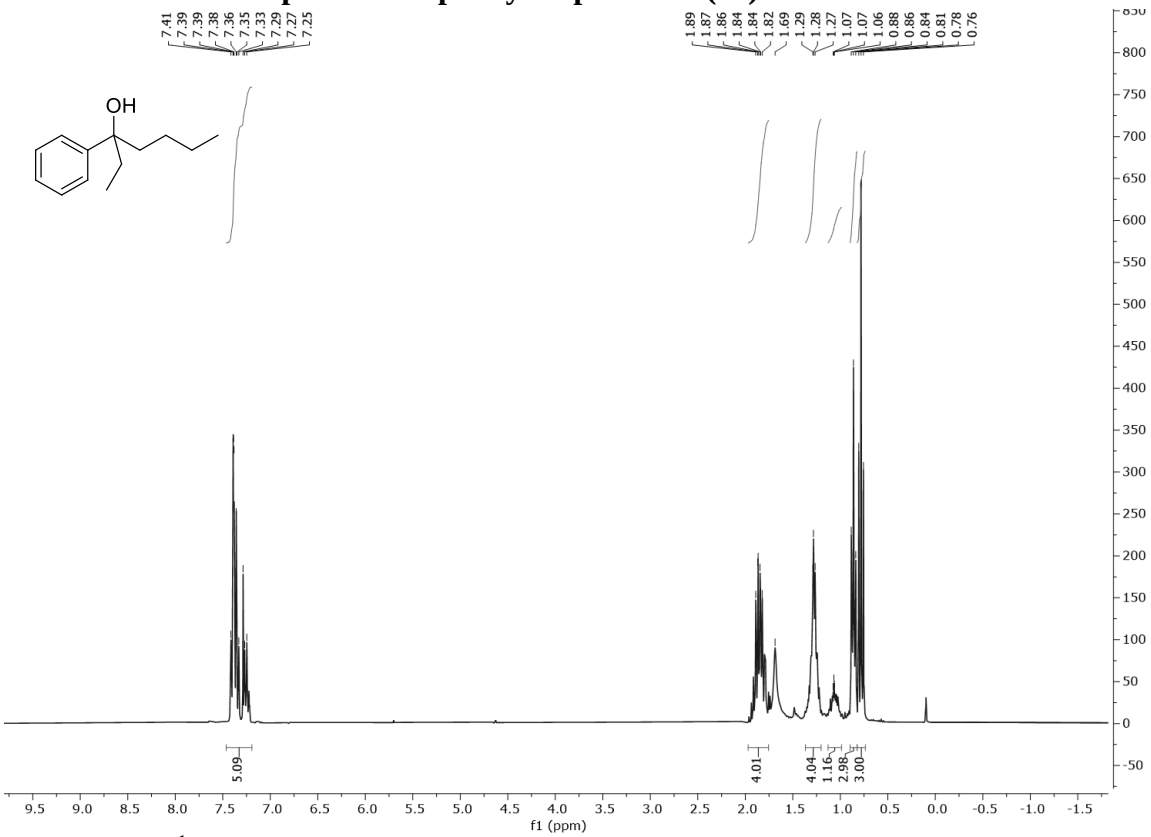


Figure S1. ^{1}H-NMR full chart for **3a** in $CDCl_3$.

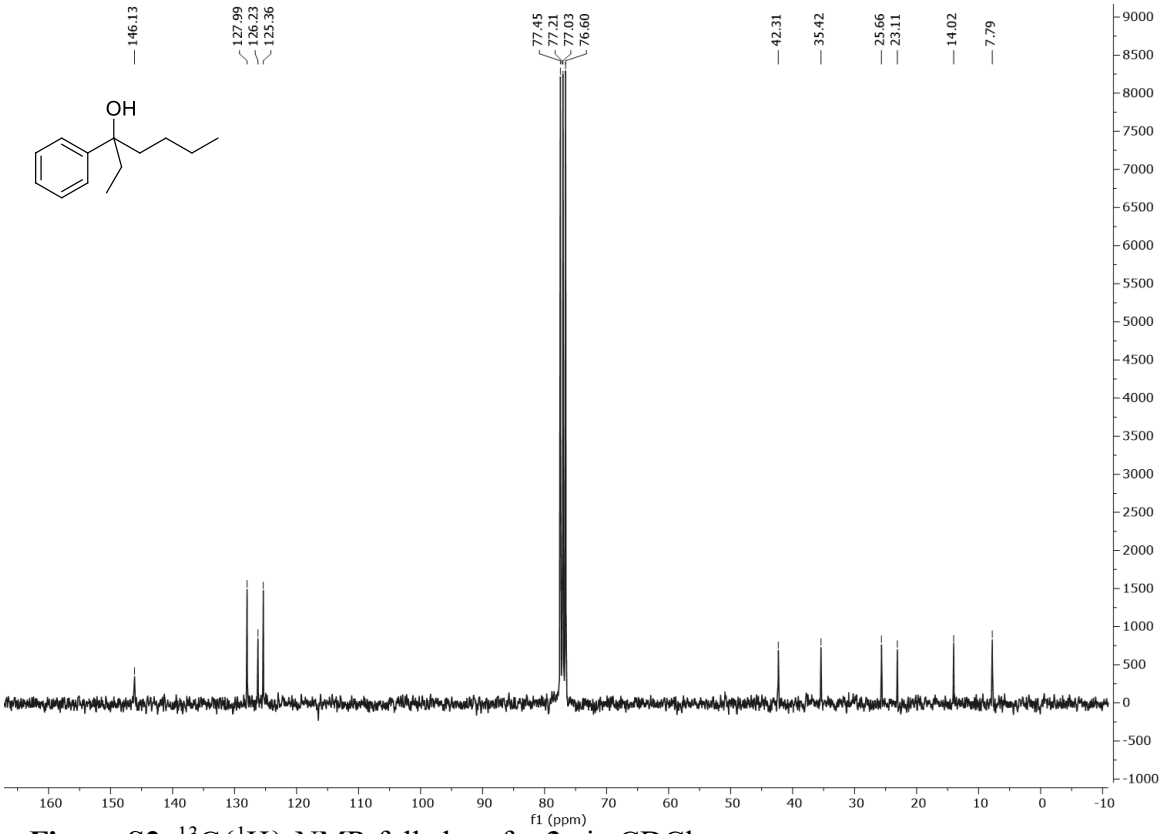


Figure S2. $^{13}C\{^{1}H\}$-NMR full chart for **3a** in $CDCl_3$.

^{1}H and ^{13}C NMR spectra of 2-phenylbutan-2-ol (3b)

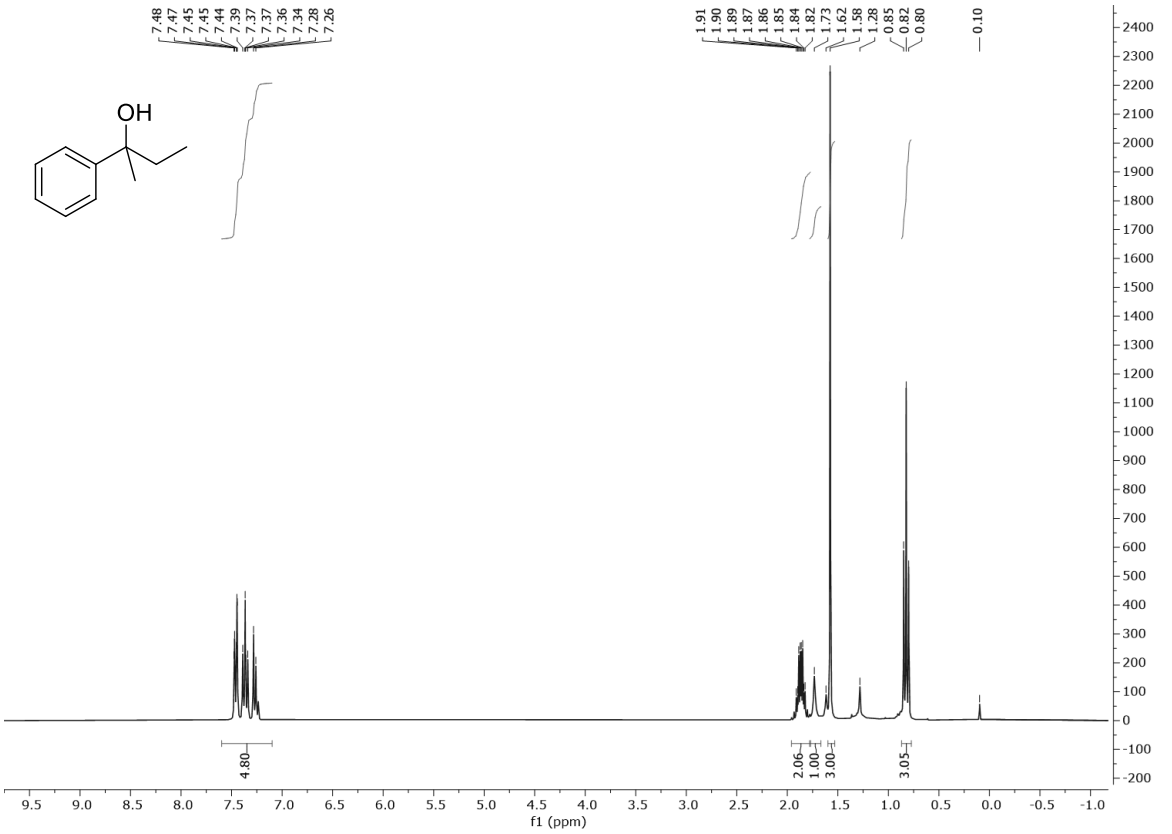


Figure S3. ^{1}H-NMR full chart for **3b** in $CDCl_3$.

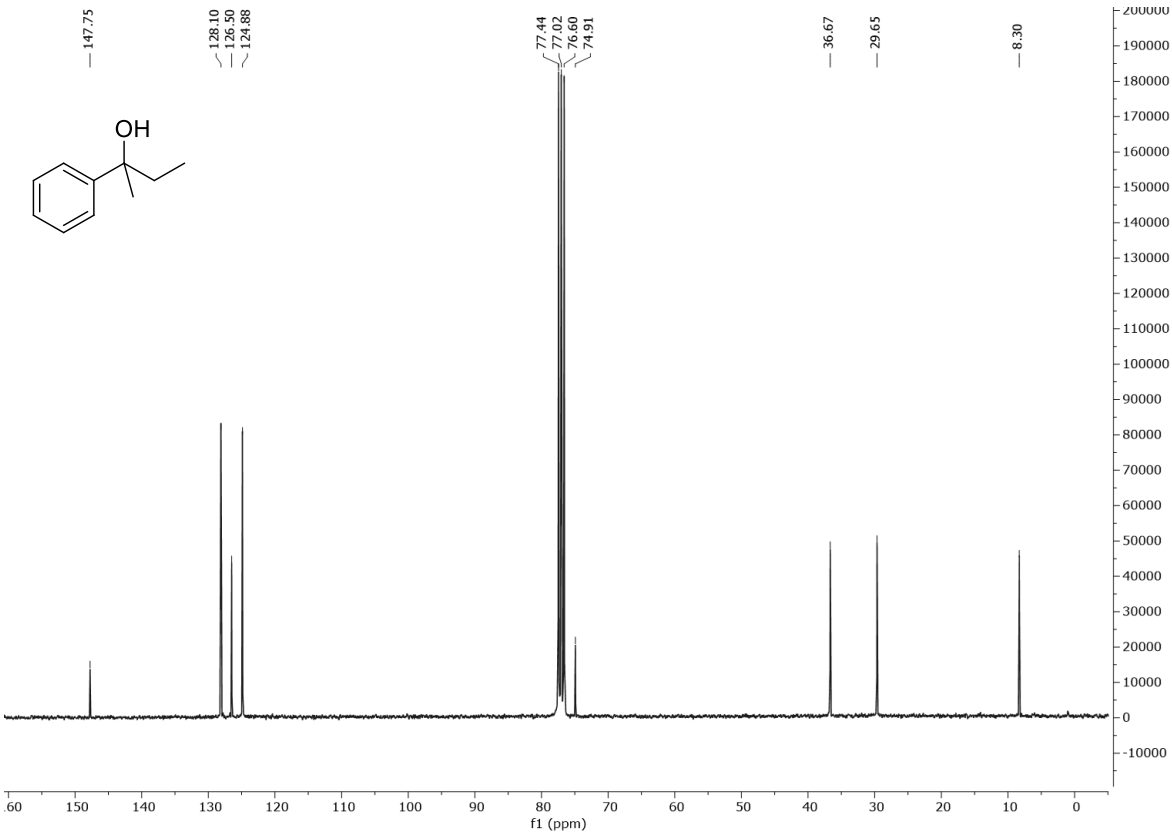


Figure S4. ^{13}C{^{1}H}-NMR full chart for **3b** in $CDCl_3$.

^{1}H and ^{13}C NMR spectra of 4-methyl-3-phenyl-hexan-3-ol (3c)

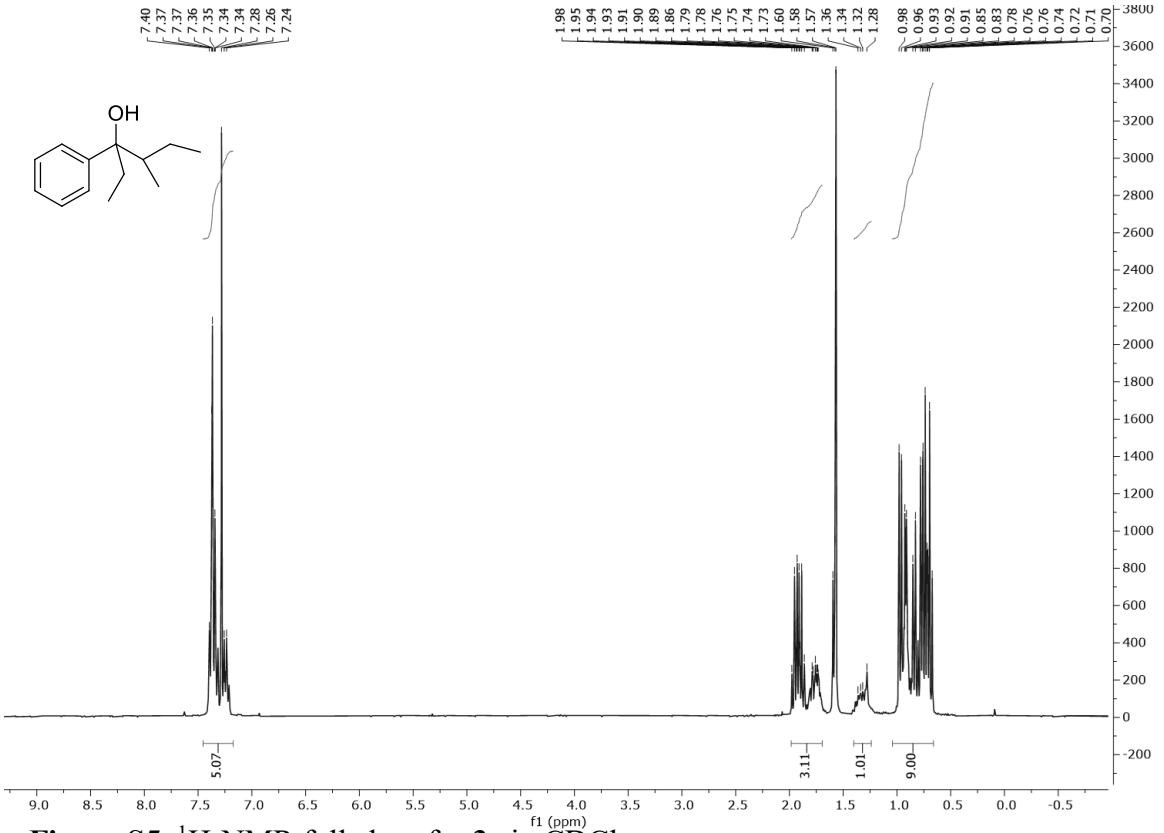


Figure S5. ^{1}H-NMR full chart for **3c** in $CDCl_3$.

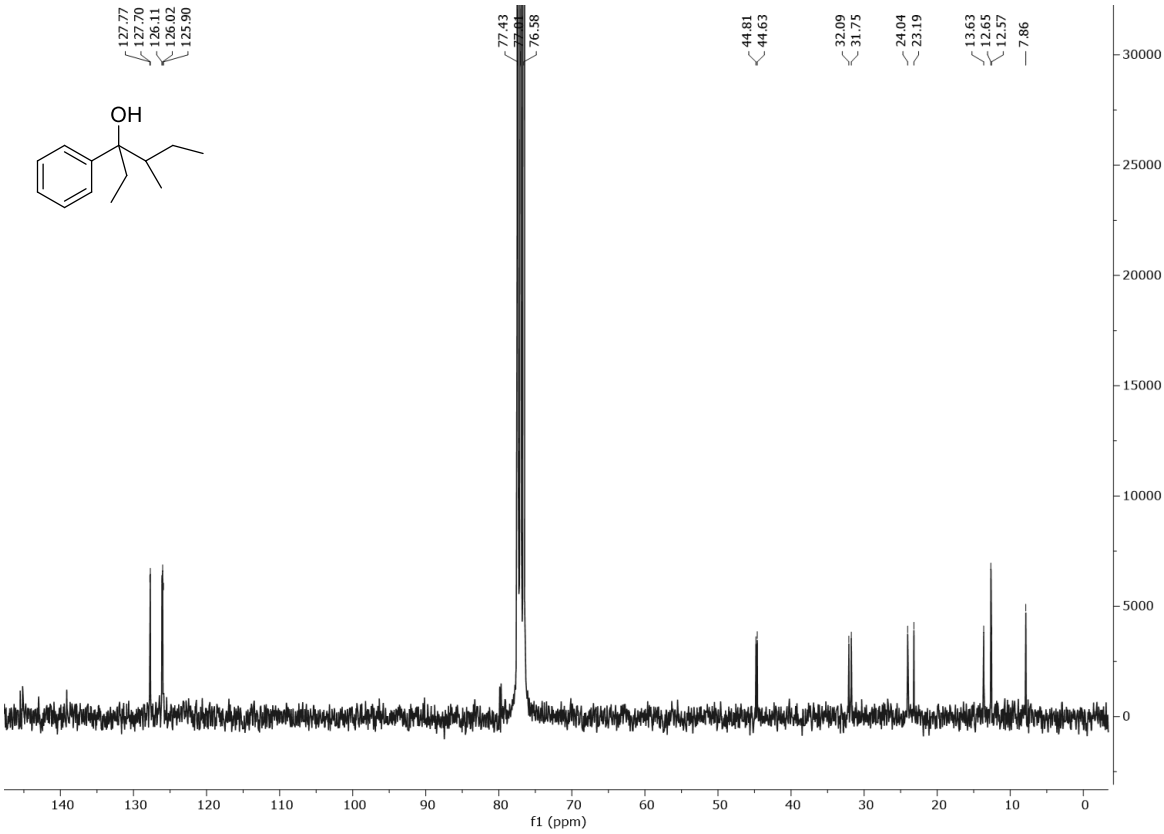


Figure S6. ^{13}C{^{1}H}-NMR full chart for **3c** in $CDCl_3$.

^{1}H and ^{13}C NMR spectra of 2,2-dimethyl-3-phenylpentan-3-ol (3d)

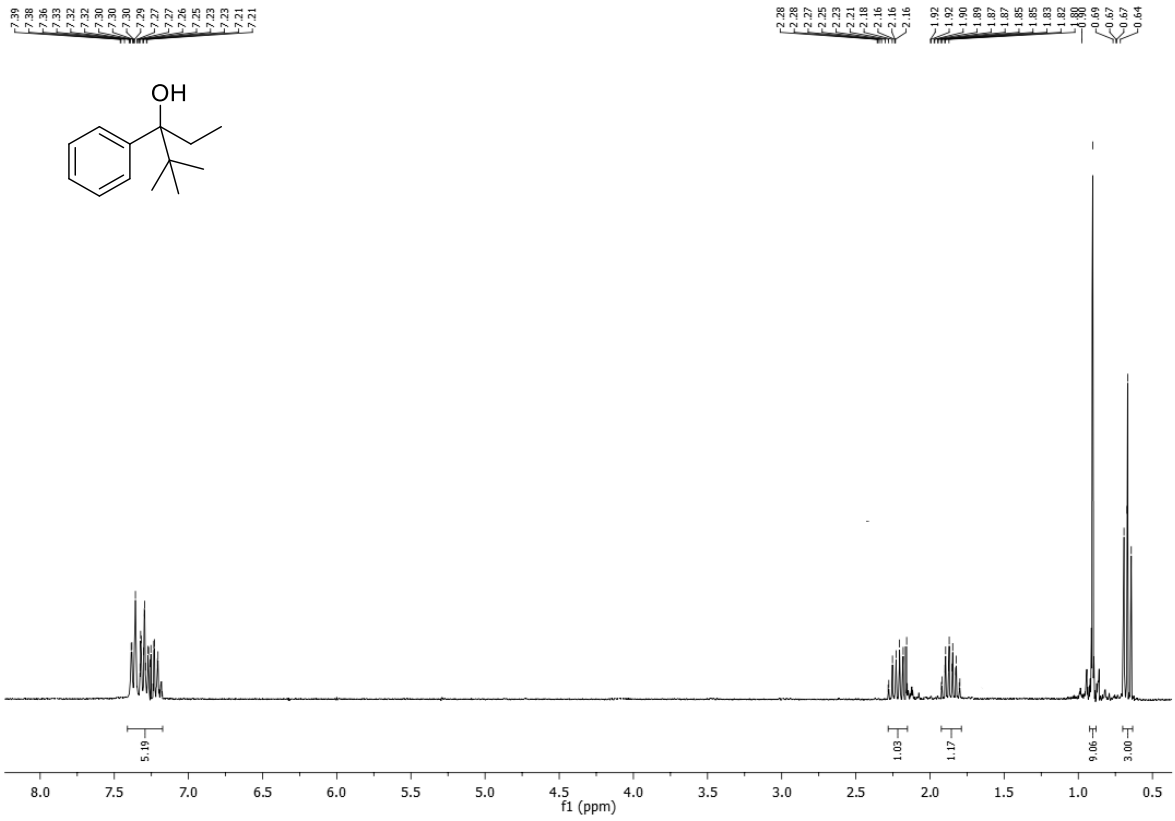


Figure S7. ^{1}H-NMR full chart for **3d** in $CDCl_3$

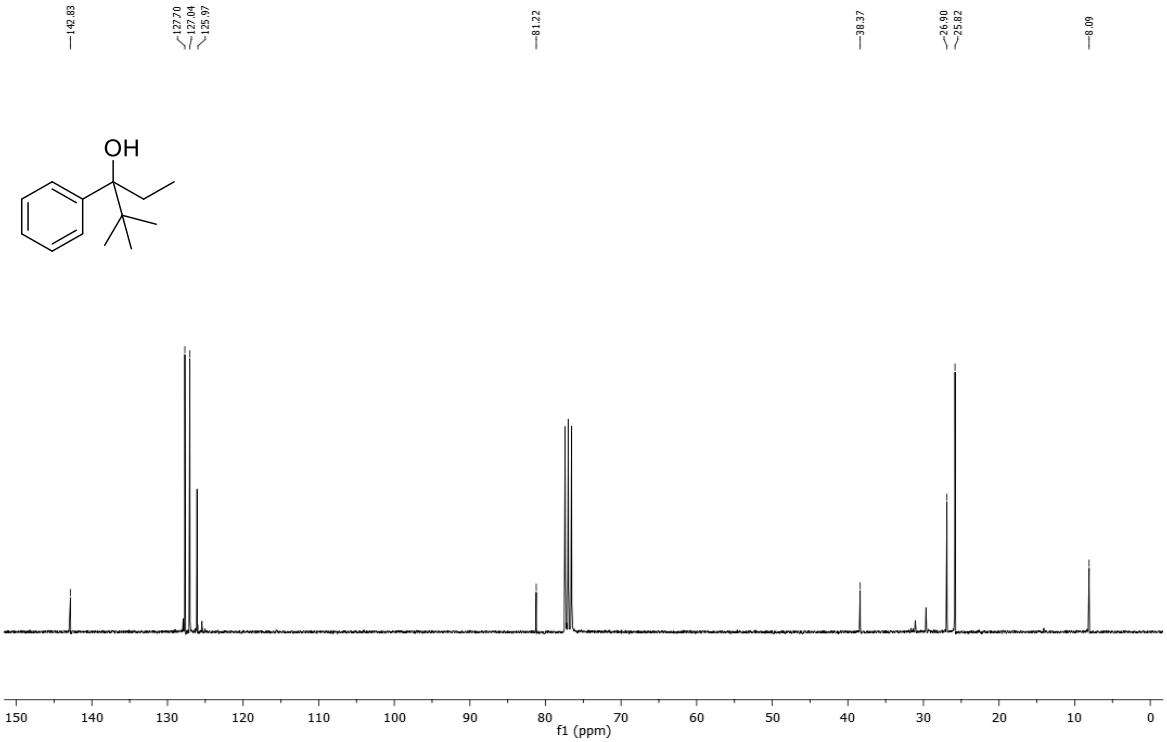


Figure S8. $^{13}C\{^{1}H\}$-NMR full chart for **3d** in $CDCl_3$.

^{1}H and ^{13}C NMR spectra of 4-methyl-3-phenyl-hexan-3-ol (3e)

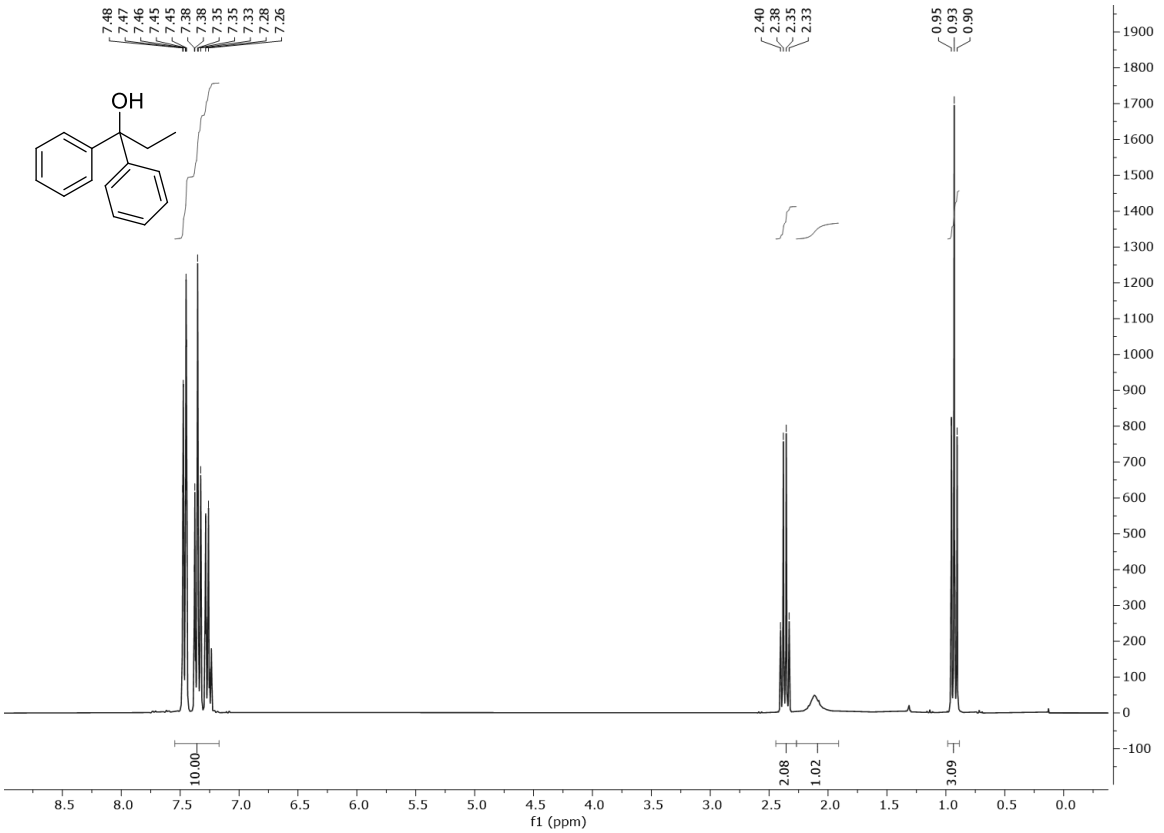


Figure S9. ^{1}H-NMR full chart for **3e** in $CDCl_3$.

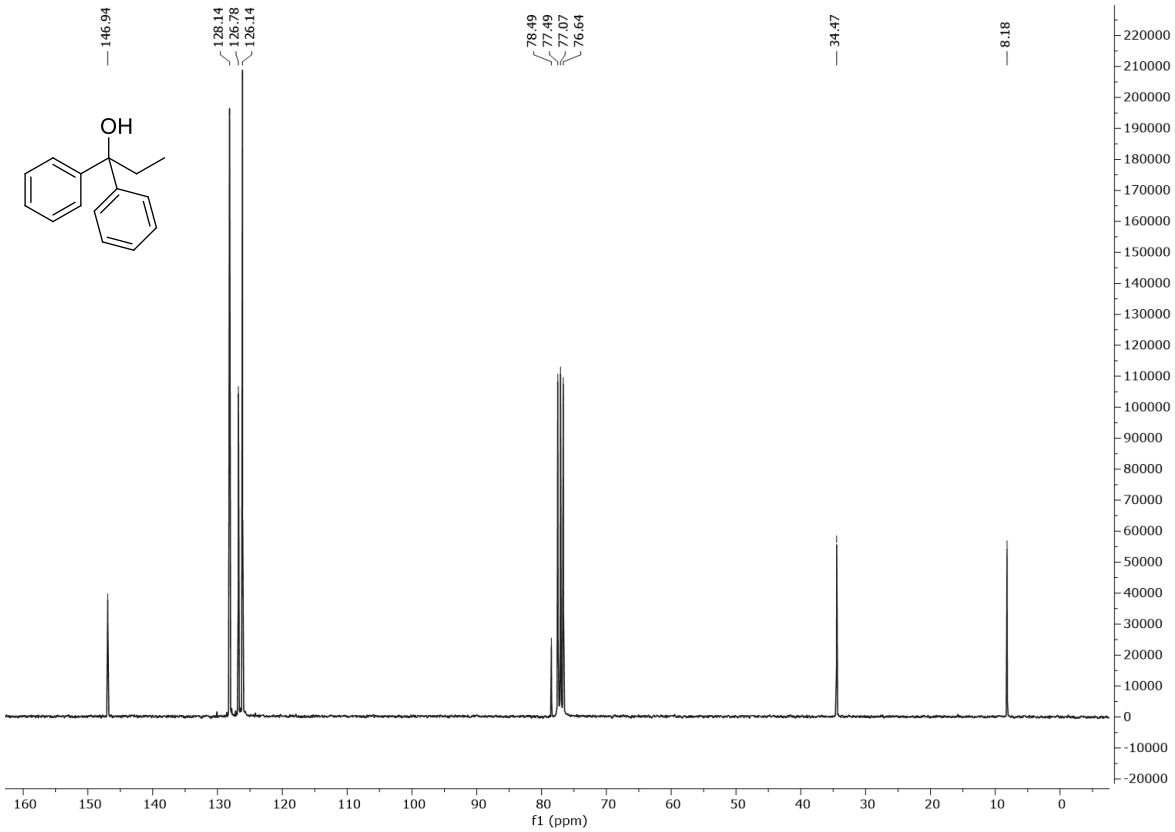


Figure S10. ^{13}C{^{1}H}-NMR full chart for **3e** in $CDCl_3$.

^{1}H and ^{13}C NMR spectra of 1,1-diphenylethan-1-ol (3f)

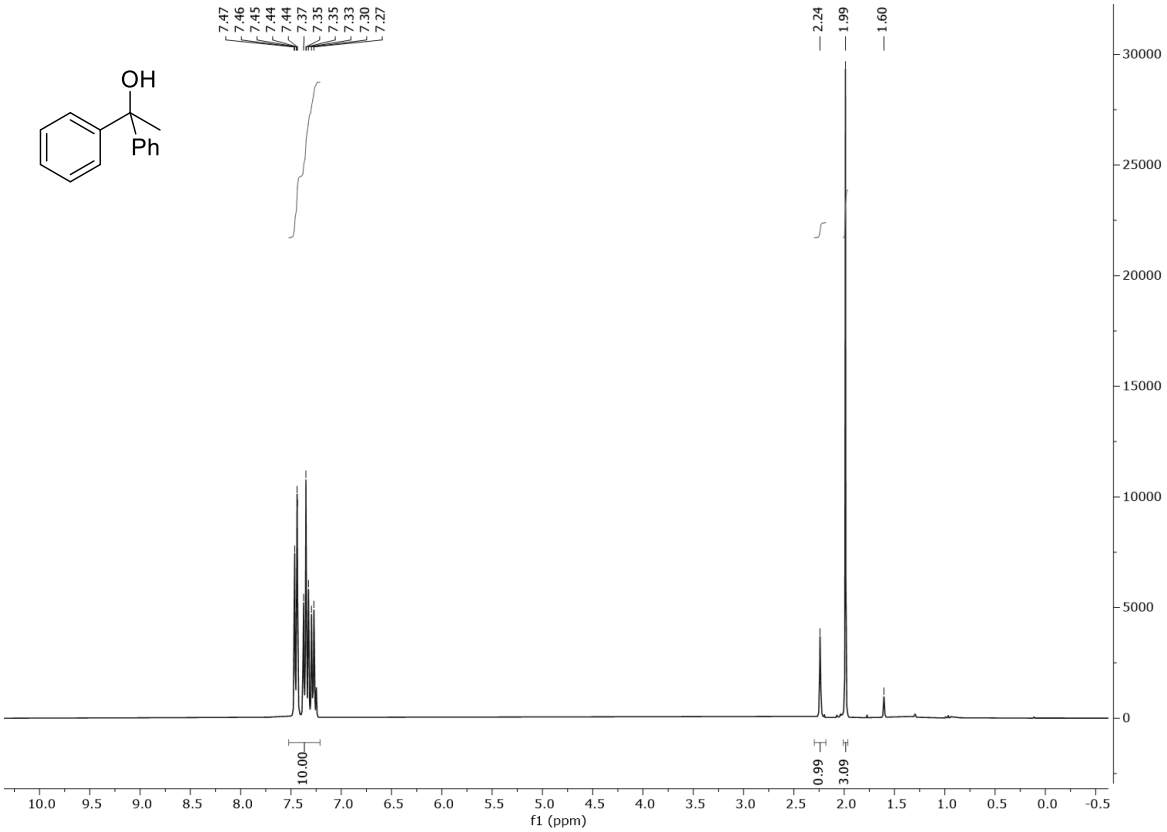


Figure S11. ^{1}H-NMR full chart for **3f** in $CDCl_3$.

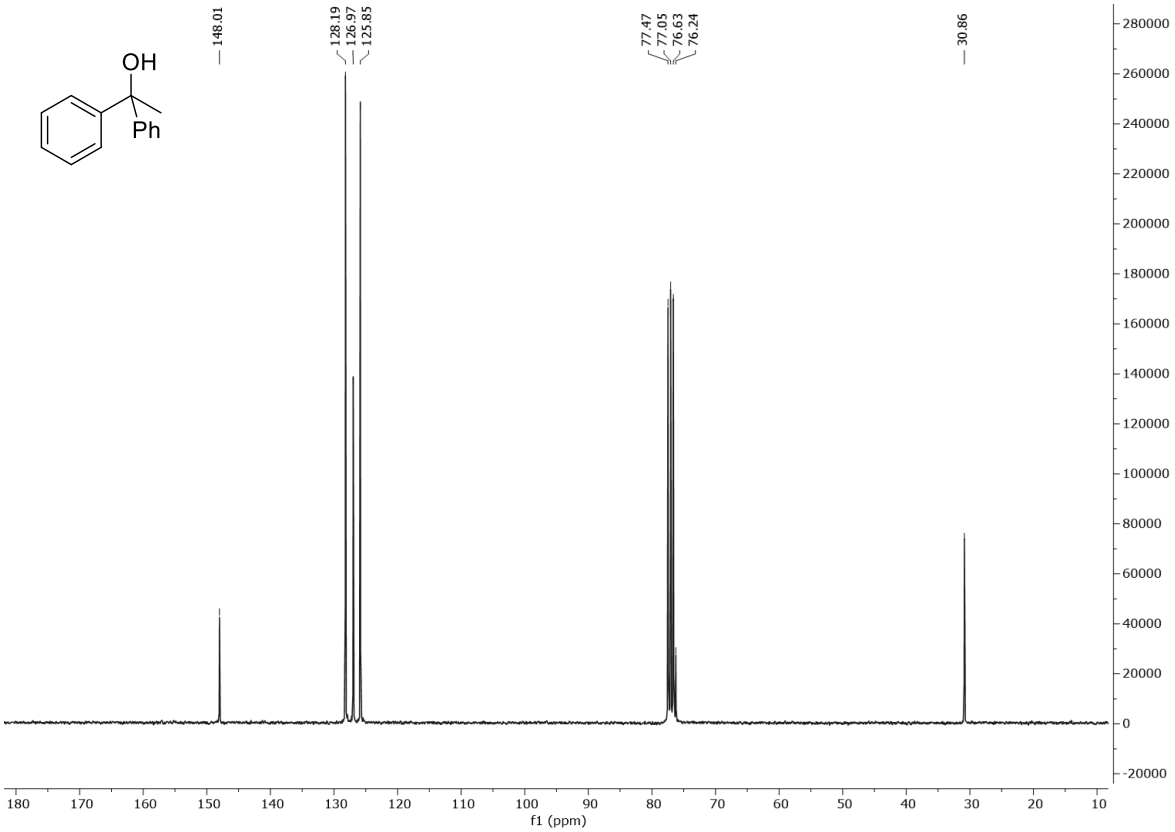


Figure S12. ^{13}C{^{1}H}-NMR full chart for **3f** in $CDCl_3$.

^{1}H and ^{13}C NMR spectra of 1-(4-chlorophenyl)-1-phenylpropan-1-ol (3g)

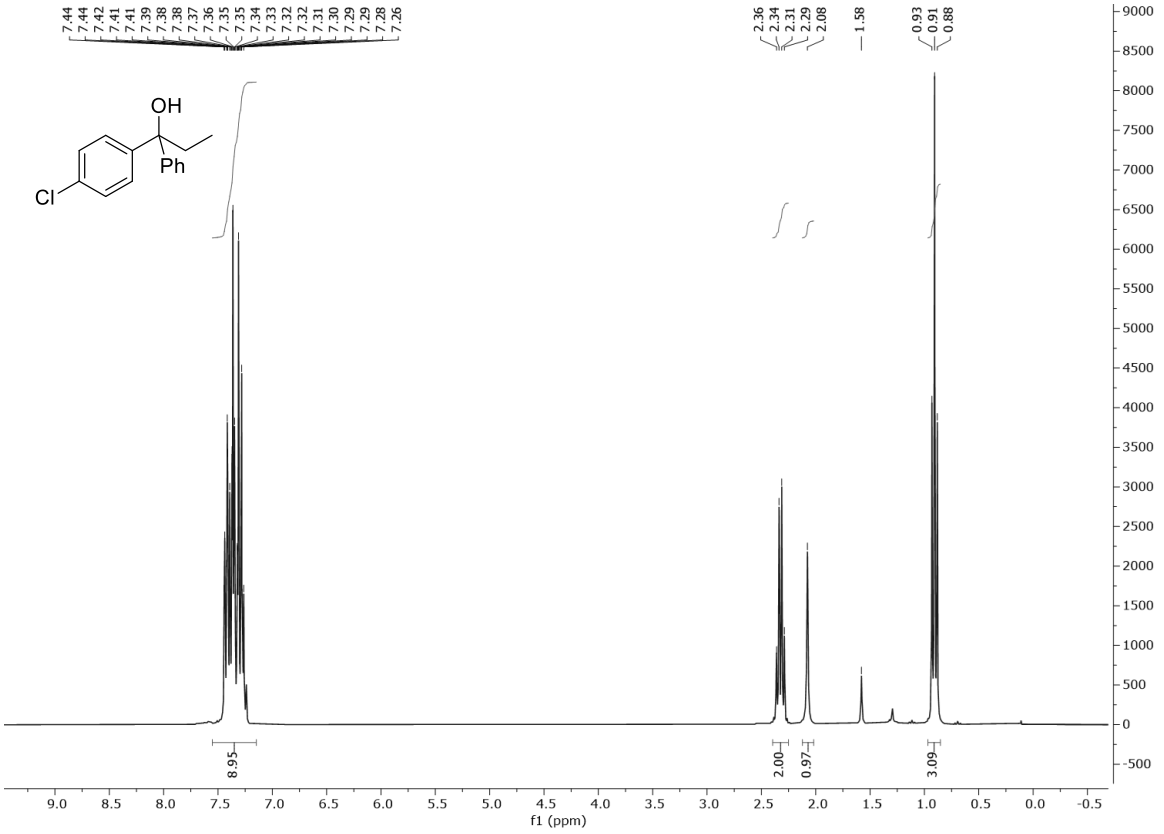


Figure S13. ^{1}H-NMR full chart for **3g** in $CDCl_3$.

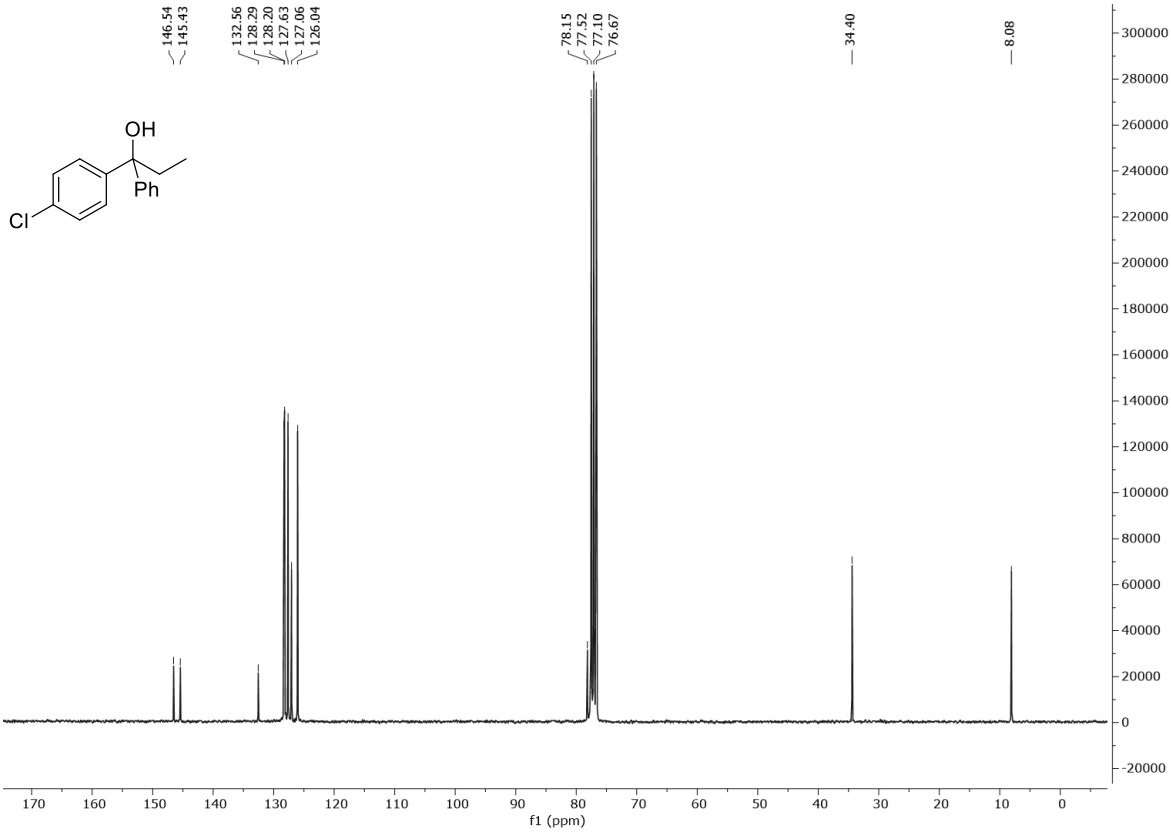


Figure S14. ^{13}C{^{1}H}-NMR full chart for **3g** in $CDCl_3$.

^{1}H and ^{13}C NMR spectra of 1-(4-bromophenyl)-1-phenylethan-1-ol (3h)

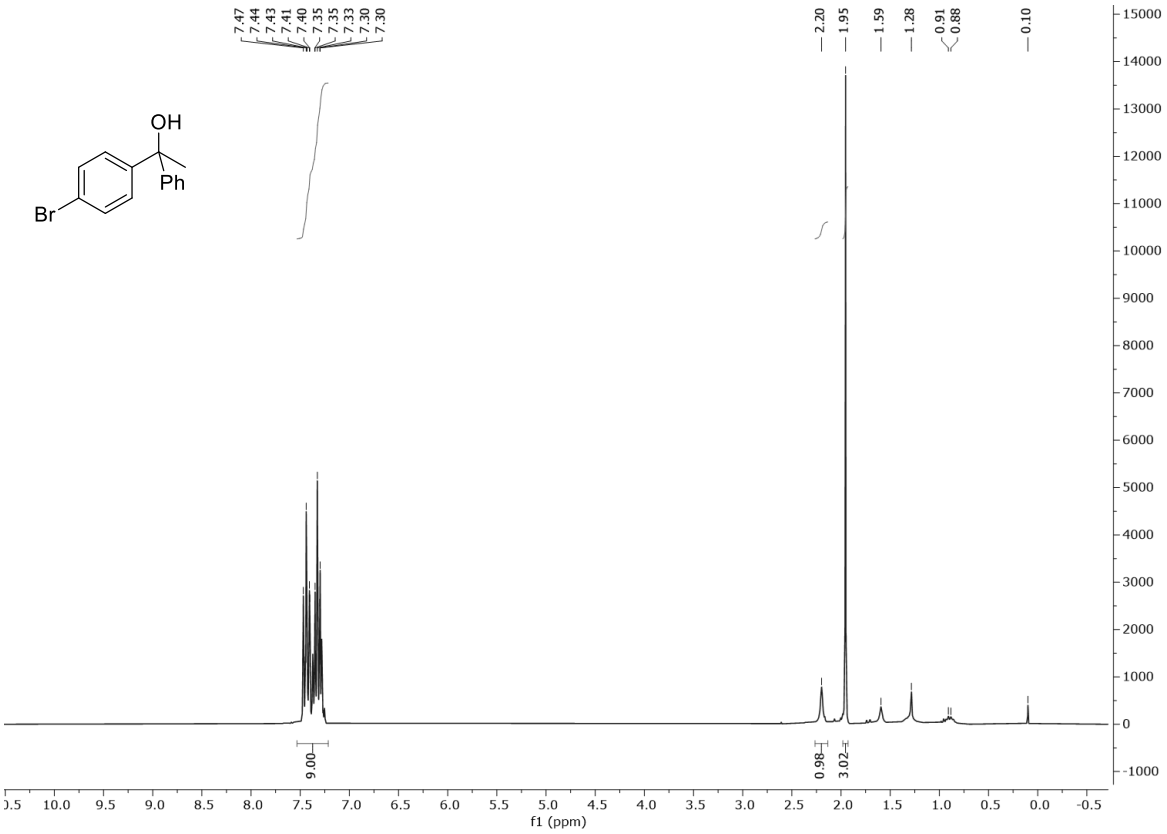


Figure S15. ^{1}H-NMR full chart for **3h** in $CDCl_3$.

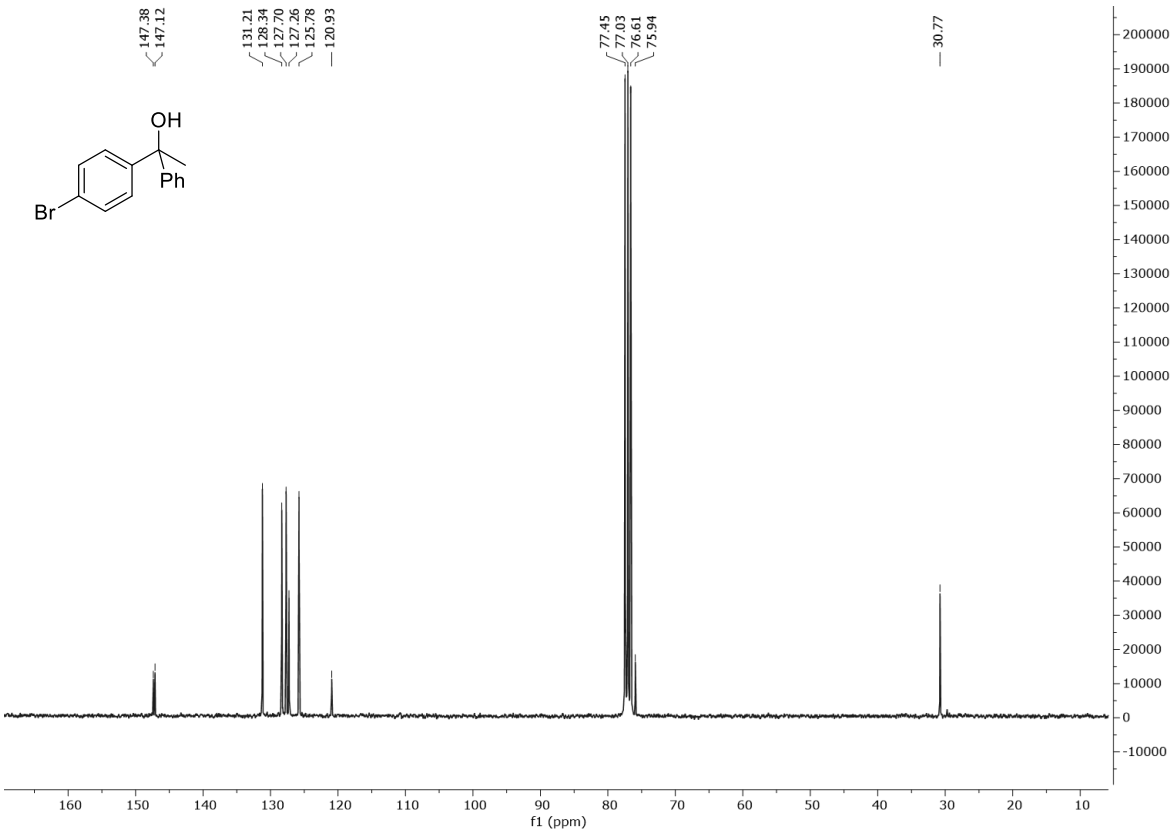


Figure S16. ^{13}C{^{1}H}-NMR full chart for **3h** in $CDCl_3$.

^{1}H and ^{13}C NMR spectra of 1-phenyl-1-(p-tolyl)propan-1-ol (3i)

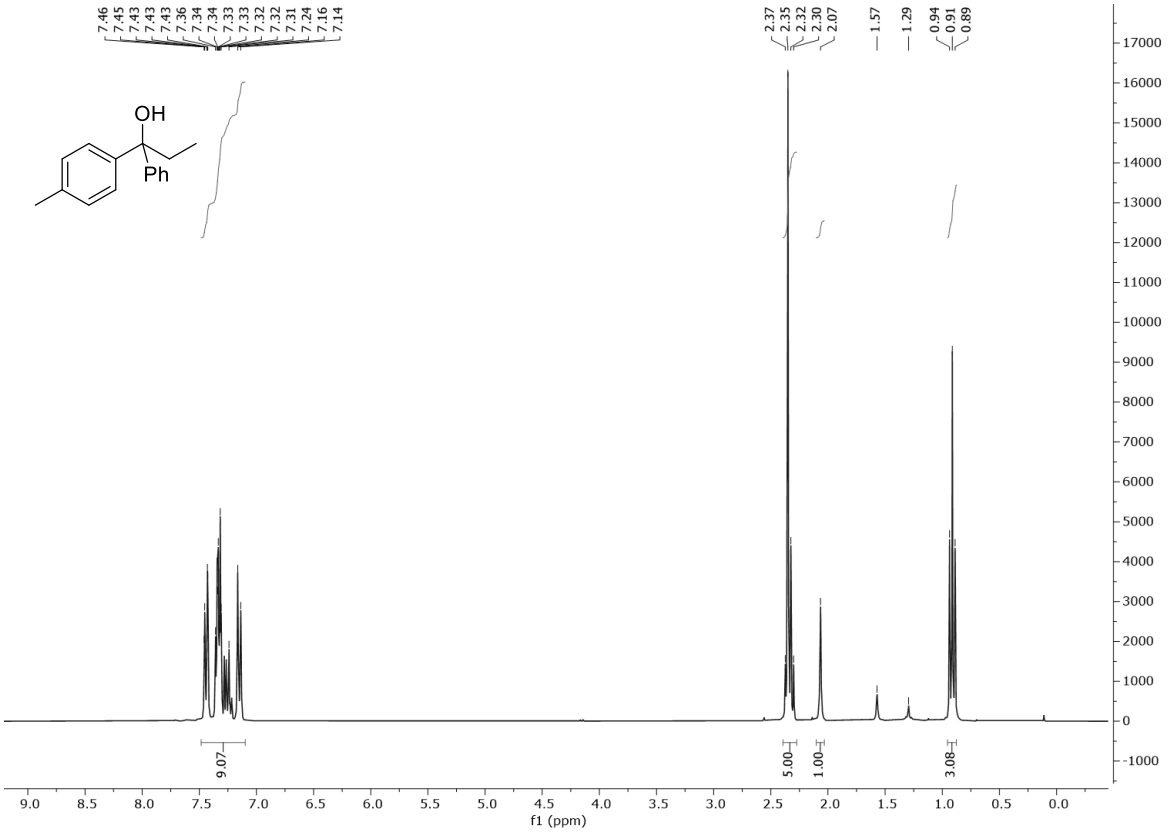


Figure S17. ^{1}H-NMR full chart for **3i** in $CDCl_3$.

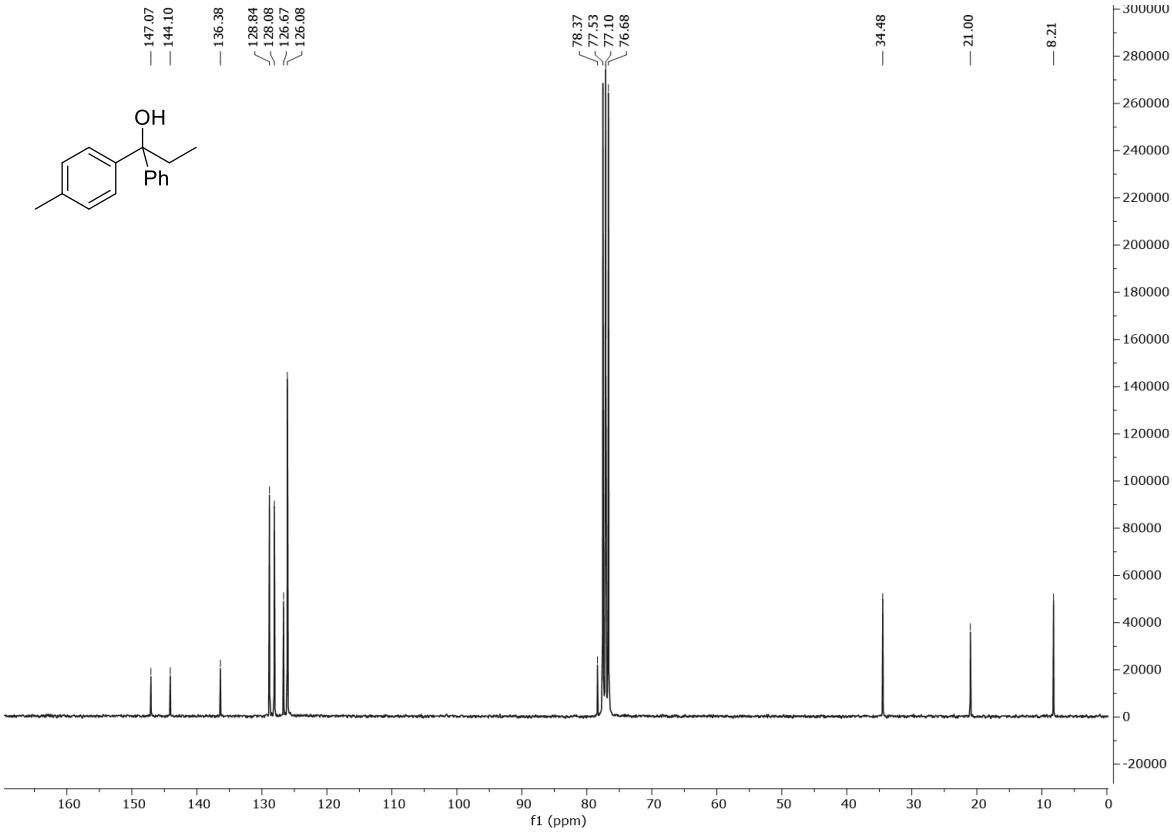


Figure S18. ^{13}C{^{1}H}-NMR full chart for **3i** in $CDCl_3$.

^{1}H and ^{13}C NMR spectra of 1-phenyl-1-(o-tolyl)ethan-1-ol (3j)

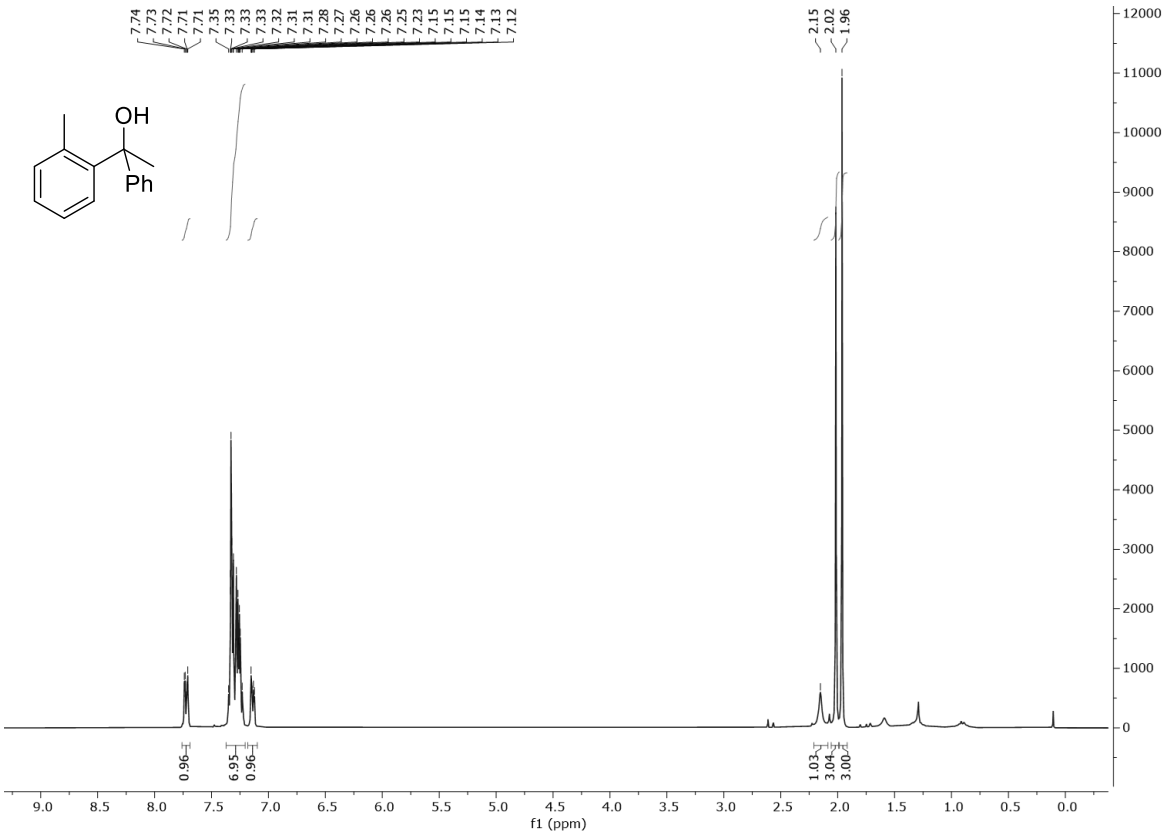


Figure S19. ^{1}H-NMR full chart for **3j** in $CDCl_3$.

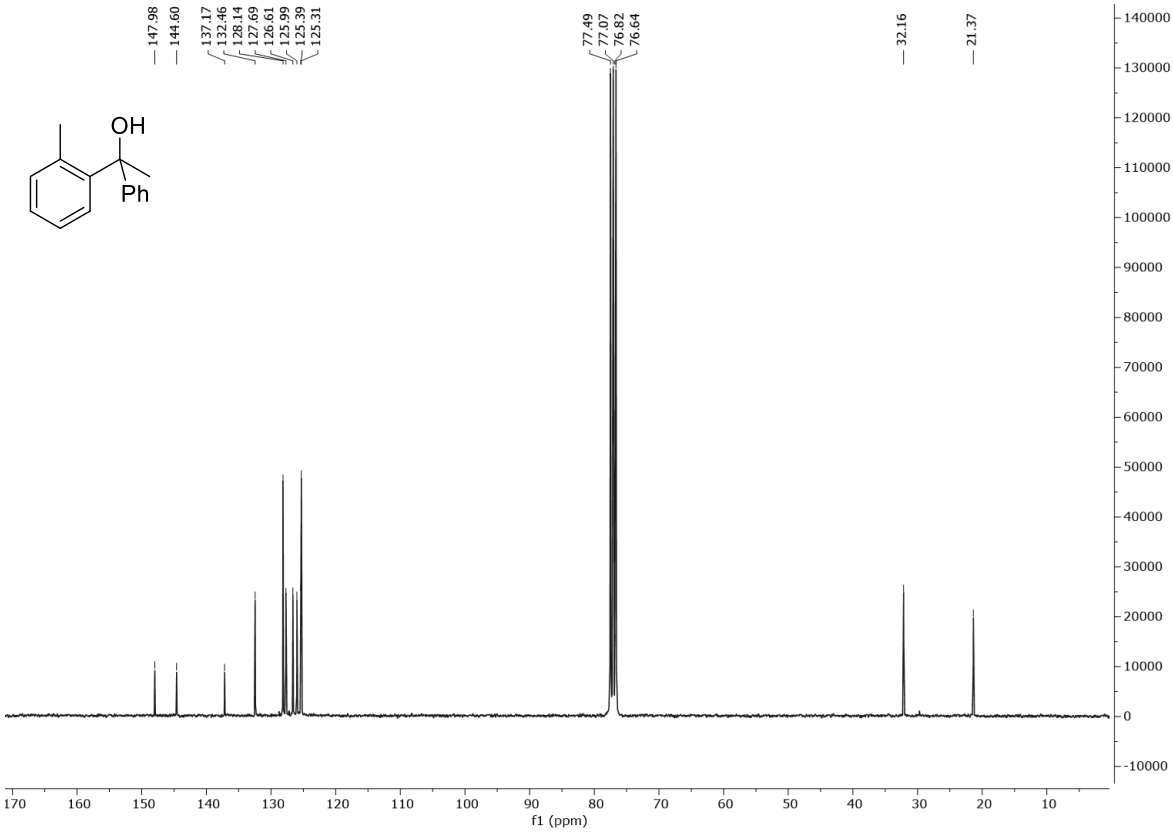


Figure S20. ^{13}C{^{1}H}-NMR full chart for **3j** in $CDCl_3$

5.- Infrared spectra of compounds 3g and 3j

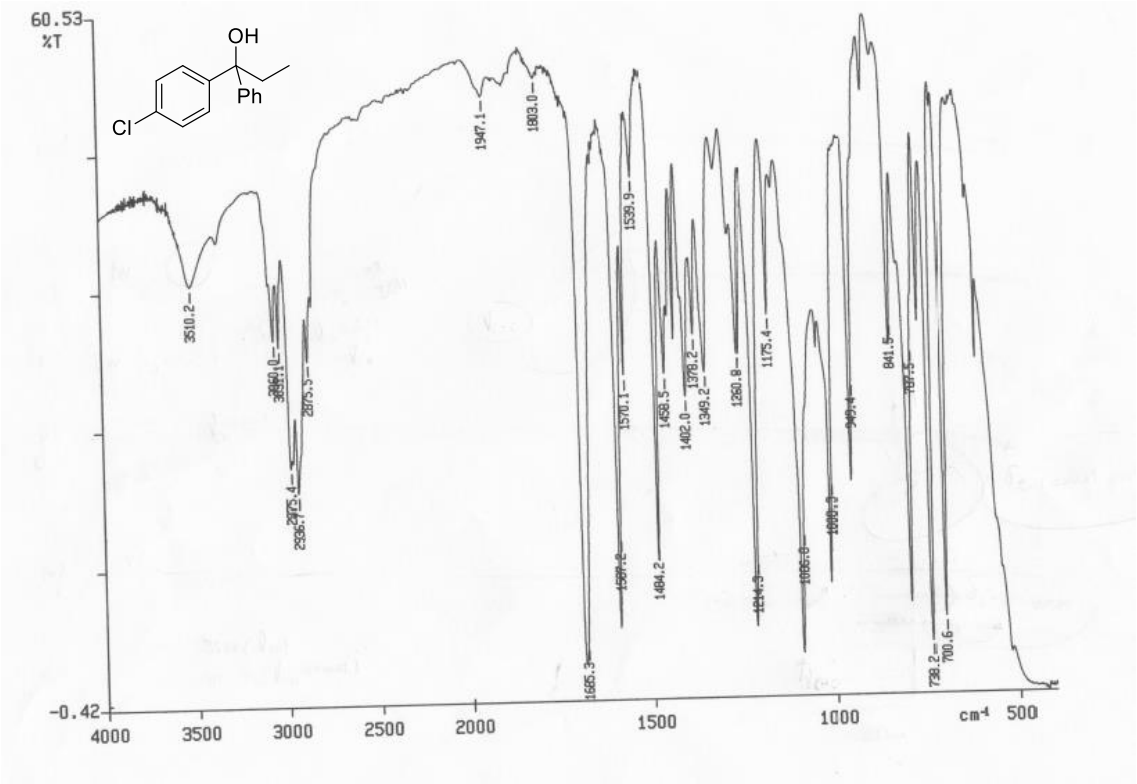


Figure S21. Infrared spectra of **3g**.

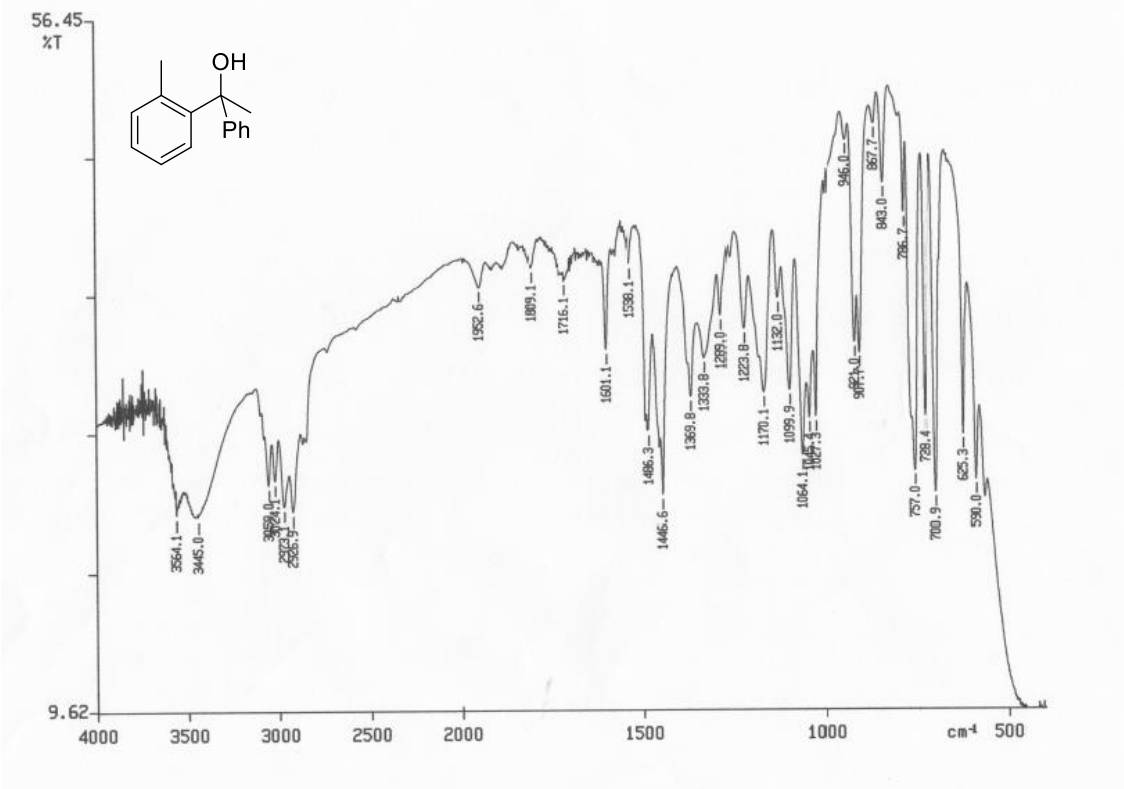


Figure S22. Infrared spectra of **3j**.

6.- References

[1] (a) S. C. Watson and J. F. Eastham, *J. Organomet. Chem.,* 1967, **9**, 165; (b) H.-S. Lin and L. A. Paquette, *Synth. Commun.,* 2007, **24**, 2503.

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