Synthesis and Exploration of Electronically Modified (*R*)-5,5-Dimethyl-(*p*-CF_3)$_3$-*i*-PrPHOX in Palladium-Catalyzed Enantio- and Diastereoselective Allylic Alkylation: A Practical Alternative to (*R*)-(*p*-CF_3)$_3$-*t*-BuPHOX

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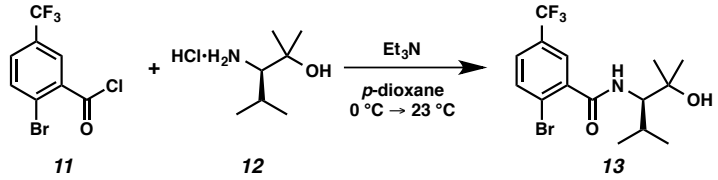
Materials and Methods

Unless stated otherwise, reactions were performed at ambient temperature (23 °C) in flame-dried or oven-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina)[1] stirring with a Teflon®-coated magnetic stirring bar. Commercially available reagents were used as received unless otherwise noted. TBAT was triturated with bench-top EtOAc (25 g batches, 2 x 100 mL washes) under a cone of argon, dried in vacuo (ca. 0.30 torr) for 24 hours, and then stored in a nitrogen-filled glovebox. Et_3N was distilled from calcium hydride immediately prior to use. Purified H_2O was obtained using a Barnstead NANOpure Infinity UV/UF system. 4 Å molecular sieves were oven-dried at 120 °C for a minimum of 24 h and cooled in a desiccator to ambient temperature immediately prior to use. (*S*)-$(CF_3)_3$-*t*-BuPHOX (**(*S*)-L1**),[2] (*S*)-*t*-BuPHOX (**(*S*)-L2**),[3] (*S*)-5,5-diphenyl-*i*-PrPHOX (**(*S*)-L3**),[4] (*R*)-5,5-dimethyl-*i*-PrPHOX (**(*R*)-L4**),[5] 2-bromo-5-(trifluoromethyl)-benzoyl chloride (**11**),[6] (*R*)-3-amino-2,4-dimethylpentan-2-ol hydrogen chloride (**12**),[4,5] bis(4-(trifluoromethyl)phenyl)phosphine oxide (**15**),[6] and tris(4,4'-methoxydibenzylideneacetone)-dipalladium(0) ($Pd_2(pmdba)_3$)[7] were prepared by known methods. Reactions requiring external heat were modulated to the specified temperatures using an IKAmag temperature controller. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (250 nm) and visualized by UV fluorescence quenching, potassium permanganate, or *p*-anisaldehyde staining. Silicycle SiliaFlash P60 Academic Silica gel (particle size 40-63 nm) was used for flash chromatography. ^1H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (500 MHz and 126 MHz, respectively) are reported in terms of chemical shift relative to residual $CHCl_3$ (in $CDCl_3$, δ 7.26 and δ 77.16, respectively) or C_6D_5H (in C_6D_6, δ 7.16 and δ 128.06, respectively). ^{19}F and ^{31}P NMR spectra were recorded on a Varian Mercury 300 spectrometer (282 MHz and 121 MHz, respectively) and are reported in terms of absolute chemical shift according to IUPAC standard recommendations from $CFCl_3$ and H_3PO_4, respectively.[8] Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Infrared (IR) spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). Analytical chiral gas chromatography was performed with an Agilent 6850 GC using a G-TA (30 m x 0.25 cm) column (1.0 mL/minute carrier gas flow). High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+) ionization mode or acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in mixed (MultiMode ESI/APCI) ionization mode. Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path length cell at 589 nm.

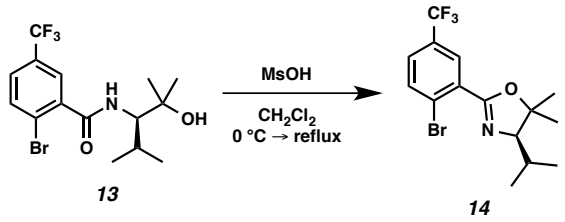
Experimental Procedures

Ligand Synthesis



Benzamide 13:[4] To a stirred solution of the hydrogen chloride salt of aminoalcohol **12** (1.00 g, 5.96 mmol, 1.00 equiv) in *p*-dioxane (20 mL) was added Et_3N (2.50 mL, 17.9 mmol, 3.00 equiv). The reaction mixture was then cooled to 0 °C (ice/H_2O bath) followed by the addition of acid chloride **11** (1.971 g, 6.86 mmol, 1.15 equiv) as a solution in *p*-dioxane (13 mL) slowly dropwise. After 15 minutes, the reaction was removed from the cooling bath and allowed to warm to ambient temperature (ca. 23 °C). After 4 h, the consumption of starting material was complete as determined by TLC (1:9 MeOH:CH_2Cl_2 eluent). The reaction mixture was concentrated in vacuo, dissolved in Et_2O, and filtered through a pad of silica gel, eluting the product with Et_2O. The filtrate was then concentrated in vacuo and the crude white solid residue was purified by silica gel column chromatography (20% acetone in hexanes eluent) to provide amide **13** (1.79 g, 79% yield) as an amorphous white solid: R_f = 0.20 (1:4 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.78–7.71 (m, 2H), 7.52 (ddt, *J* = 8.3, 2.3, 0.7 Hz, 1H), 6.40 (d, *J* = 10.3 Hz, 1H), 4.03 (dd, *J* = 10.1, 2.6 Hz, 1H), 2.27 (dtd, *J* = 13.7, 6.8, 2.6 Hz, 1H), 1.37 (s, 3H), 1.34 (s, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 167.0, 139.4, 134.3, 130.4 (q, *J* = 33.5 Hz), 127.7 (q, *J* = 3.6 Hz), 126.6 (q, *J* = 3.8 Hz), 123.5 (q, *J* = 272.3 Hz), 123.2 (q, J = 1.5 Hz), 73.8, 60.9, 29.9, 28.8, 27.7, 22.5, 17.2; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –62.8 (s); IR (Neat Film, NaCl) 3413, 3299, 2964, 1638, 1540, 1332, 1311, 1173, 1132, 1080, 1033, 828 cm^{-1}; HRMS

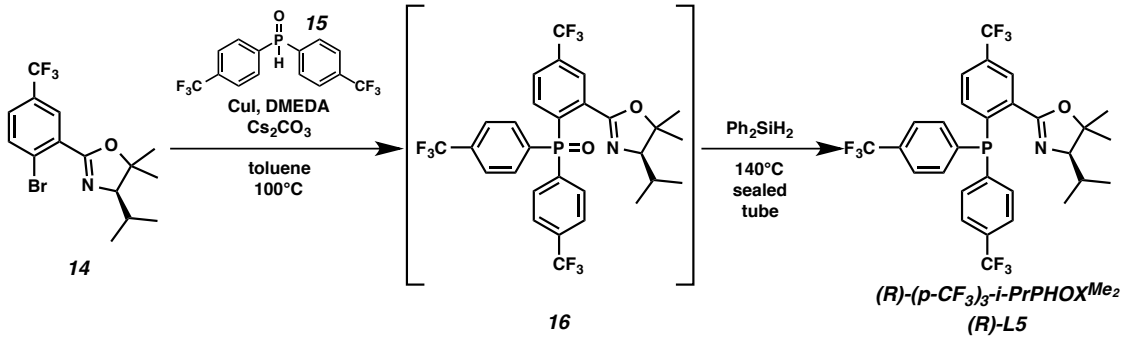
(MM: ESI-APCI) *m/z* calc'd for $C_{15}H_{20}O_2{}^{79}BrF_3N$ $[M+H]^+$: 382.0624, found 382.0633; $[\alpha]_D^{25.0}$ –3.9° (*c* 0.895, $CHCl_3$).



Oxazoline 14:[4]

To a solution of amide **13** (1.41 g, 3.70 mmol, 1.00 equiv) in CH_2Cl_2 (93 mL) at 0 °C (ice/H_2O bath) was added methanesulfonic acid (MsOH, 1.44 mL, 22.2 mmol, 6.00 equiv) dropwise over 10 minutes. The flask was subsequently removed from the cooling bath, fitted with a reflux condenser, and introduced to a preheated 50 °C bath. After 17 h, the consumption of starting material was complete as determined by TLC (1:4 Acetone:Hexanes eluent). The refluxing solution was removed from the heating bath and allowed to cool to ambient temperature (ca. 23 °C). The yellow reaction mixture was then diluted with CH_2Cl_2 (100 mL) and poured onto saturated aqueous $NaHCO_3$ (100 mL). The organics were separated and washed with H_2O (40 mL) and brine (40 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude gold oil was purified by silica gel column chromatography (5%→10% acetone in hexanes eluent) to provide oxazoline **14** (1.18 g, 87% yield) as a pale yellow oil: R_f = 0.42 (1:9 Et_2O:Hexanes eluent); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.92–7.88 (m, 1H), 7.77–7.72 (m, 1H), 7.52–7.46 (m, 1H), 3.53 (d, *J* = 8.1 Hz, 1H), 1.94 (dhept, *J* = 8.0, 6.6 Hz, 1H), 1.56 (s, 3H), 1.45 (s, 3H), 1.16 (d, *J* = 6.5 Hz, 3H), 1.05 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 160.4, 134.6, 131.6, 129.8 (q, *J* = 33.4 Hz), 128.4 (q, *J* = 3.8 Hz), 127.9 (q, *J* = 3.6 Hz),

126.1 (q, J = 1.7 Hz), 123.5 (q, J = 272.8 Hz), 88.2, 81.0, 29.4, 29.2, 21.4, 21.3, 20.7; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –62.8 (s); IR (Neat Film, NaCl) 2973, 1652, 1608, 1472, 1343, 1306, 1173, 1133, 1077, 1028, 830 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{15}H_{18}O^{79}BrF_3N$ $[M+H]^+$: 364.0518, found 364.0535; $[\alpha]_D^{25.0}$ +33.1° (*c* 6.050, $CHCl_3$).



(*R*)-5,5-dimethyl-(p-CF_3)$_3$-i-PrPHOX ((*R*)-L5):[2a]

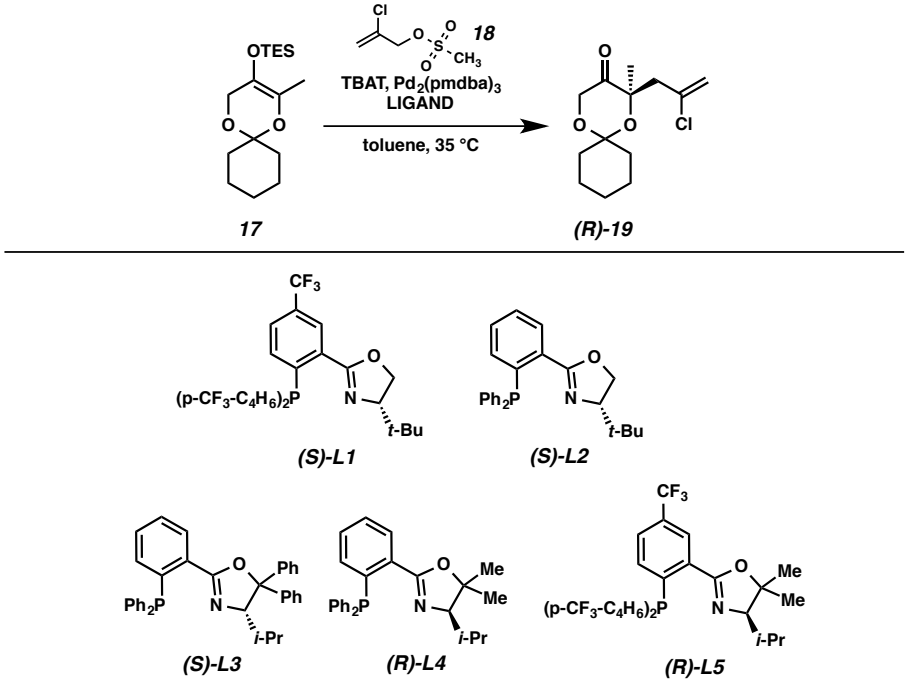
To a multineck reaction vessel fitted with a reflux condenser were added CuI (377 mg, 1.98 mmol, 1.00 equiv) and phosphine oxide **15** (870 mg, 2.57 mmol, 1.30 equiv) as solids. The reaction vessel was then evacuated and backfilled with argon (3 x 5 minute cycles). Toluene (8 mL) was then added and stirring commenced. *N,N'*-Dimethylethylenediamine (DMEDA, 0.64 mL, 5.94 mmol, 3.00 equiv) was then added dropwise causing the yellow heterogeneous reaction mixture to become dark green and homogeneous. After 20 minutes, oxazoline **14** (721 mg, 1.98 mmol, 1.00 equiv) was added as a neat oil dropwise followed by Cs_2CO_3 (2.39 g, 7.33 mmol, 3.70 equiv) as a solid in a single portion. The reaction vessel was then introduced to a preheated 110 °C bath. After 20 h, the consumption of starting material was complete as determined by TLC (1:9 Et_2O:Hexanes eluent). The refluxing solution was removed from the heating bath and allowed to cool to ambient temperature (ca. 23 °C). The crude reaction mixture

was concentrated in vacuo and the crude brown solid was purified by silica gel column chromatography (25%→50% EtOAc in hexanes eluent) to provide phosphine oxide **16** (778 mg, 63% yield) as an amorphous white solid that was carried directly into the next transformation.

Solid phosphine oxide **16** (778 mg, 1.25 mmol, 1.00 equiv) was added to a sealable pressure vessel, which was then evacuated and backfilled with argon (3 x 5 minute cycles). To the flask was then added Ph_2SiH_2 (1.63 mL, 8.76 mmol, 7.00 equiv) with stirring. The reaction vessel, containing a homogeneous yellow solution, was then sealed and introduced to a preheated 140 °C bath. After 48 h, the consumption of starting material was complete as determined by TLC (1:1 EtOAc:Hexanes eluent). The refluxing solution was removed from the heating bath and allowed to cool to ambient temperature (ca. 23 °C). The crude reaction mixture was directly purified by silica gel column chromatography (20% CH_2Cl_2 in hexanes eluent) to furnish (*R*)-5,5-dimethyl-(*p*-CF_3)$_3$-i-PrPHOX ((*R*)-(*p*-CF_3)$_3$-*i*-PrPHOX^{Me_2}, **(*R*)-L5**, 614 mg, 81% yield) as an amorphous white solid: R_f = 0.27 (1:4 CH_2Cl_2:Hexanes eluent); ^{1}H NMR (C_6D_6, 500 MHz) δ 8.57 (dd, *J* = 3.3, 2.0 Hz, 1H), 7.41–7.36 (m, 4H), 7.21–7.15 (m, 4H), 7.10 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.78 (dd, *J* = 8.0, 3.0 Hz, 1H), 3.22 (d, *J* = 8.4 Hz, 1H), 1.55 (ddt, *J* = 13.0, 8.3, 6.5 Hz, 1H), 1.21 (s, 3H), 1.08 (s, 3H), 0.99 (d, *J* = 6.5 Hz, 3H), 0.75 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (C_6D_6, 126 MHz) δ 159.1 (d, *J* = 4.0 Hz), 143.5 (t, *J* = 14.8 Hz), 142.7 (d, *J* = 30.6 Hz), 134.5 (dd, *J* = 21.3, 15.7 Hz), 133.7 (d, *J* = 19.5 Hz), 131.1 (q, *J* = 33.1 Hz), 131.0 (dq, *J* = 32.3, 4.4 Hz), 127.1 (q, *J* = 3.6 Hz), 126.4–126.1 (m), 125.5 (dp, *J* = 7.5, 3.8 Hz), 124.8 (dq, *J* = 272.0, 3.3 Hz), 124.4 (q, *J* = 272.6 Hz), 87.2, 81.7 (d, *J* = 1.5 Hz), 29.1, 28.8, 21.1, 20.8, 20.8 (d, *J* = 1.8 Hz); ^{19}F NMR (C_6D_6, 282 MHz) δ –62.6 (s), –62.9

(s); ^{31}P NMR (C_6D_6, 121 MHz) δ –7.1 (s); IR (Neat Film, NaCl) 2974, 1652, 1606, 1397, 1323, 1165, 1128, 1060, 1017, 832, 756 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{29}H_{26}OF_9NP$ $[M+H]^+$: 606.1608, found 606.1585; $[\alpha]_D^{25.0}$ +9.5° (*c* 3.200, $CHCl_3$).

General Procedure for Intermolecular Asymmetric Allylic Alkylation



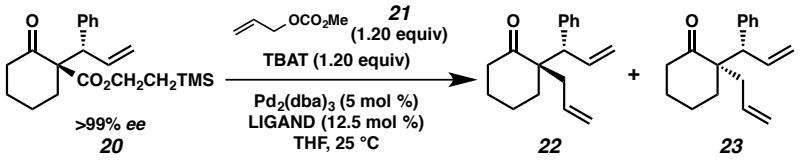
Entry	Ligand	Amino Acid Ligand Precursor	Amino Acid Cost per gram ($) [a] *S* - Enantiomer	*R*	Product ee (%) [b]
1	***(S)-L2***	*tert*-Leucine	33	351	–92
2	***(S)-L1***	*tert*-Leucine	33	351	–91
3	***(S)-L3***	Valine	0.60	6	–90
4	***(R)-L4***	Valine	0.60	6	89
5	***(R)-L5***	Valine	0.60	6	91

[a] Cost per gram of amino acid from Sigma-Aldrich, accessed 4/30/2015.
[b] Enantiomeric excess (*ee*) measured by analytical chiral GC.

Chloroallylketone 19: The procedure for the asymmetric allylic alkylation of enol ether **17** with mesylate **18** was adapted from our previous report.[9] A 20 mL scintillation vial was soaked in a 20:1 *i*-PrOH:toluene bath saturated with KOH for 12 h, rinsed with deionized H_2O, acetone, and allowed to dry in a 120 °C oven for an additional 12 h. To this oven-dried 20 mL scintillation vial in a nitrogen-filled glovebox were charged

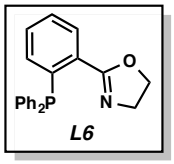
$Bu_4NPh_3SiF_2$ (TBAT, 216 mg, 0.40 mmol, 1.00 equiv), $Pd_2(pmdba)_3$ (7 mg, 0.006 mmol, 0.015 equiv), ligand (0.014 mmol, 0.035 equiv), and toluene (8.0 mL). The reaction vessel immediately placed into preheated 35 °C heating block with stirring. After 20 minutes, a yellow-brown solution was observed. Chloroallylmesylate **18** (82 mg, 0.48 mmol, 1.20 equiv) was then added quickly dropwise affording a blue-green solution. After 3 minutes, silyl enol ether **17** (120 mg, 0.40 mmol, 1.00 equiv) was added quickly dropwise. The resultant blue-green reaction mixture was allowed to stir for 20 h, at which time the consumption of starting material was complete as determined by TLC (1:19 Et_2O:Hexanes eluent). The resultant yellow-brown reaction was then allowed to cool to ambient temperature (ca. 23 °C), removed from the glovebox, filtered through a pad of SiO_2 using hexanes as the eluent to remove toluene, at which time separate fractions were collected, eluting with Et_2O, to isolate the semi-volatile reaction products. The filtrate was concentrated in vacuo to a bright yellow oil which was subsequently purified by silica gel column chromatography (1%→3%→5% Et_2O in hexanes eluent) to afford semi-volatile chloroallylketone **19** as a clear, colorless oil. R_f = 0.41 (1:19 Et_2O:Pentane eluent); characterization data match those reported in the literature.[9] The *ee* of each product was determined by analytical chiral GC (G-TA column, 120 °C isotherm, major retention time: 53.209 min, minor retention time: 52.075 min).

General Procedure for Diastereoselective Allylic Alkylation



Entry	Ligand	% yield [a]	dr (*22* : *23*) [b]
1	*L6*	79	2:1
2	*(S)-L2*	79	1:2
3	*(R)-L2*	73	12:1
4	*(R)-L5*	85	18:1

[a] Isolated yield of ***22*** and ***23***. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture and analytical GC analysis



L6

Cyclohexanone 22 and Cyclohexanone 23: The procedure for the asymmetric diastereoselective allylic alkylation of β-ketoester **20** with formate **21** was performed exactly as described in our previous report.[10] The characterization data match those reported in the literature.[10]

Notes and References

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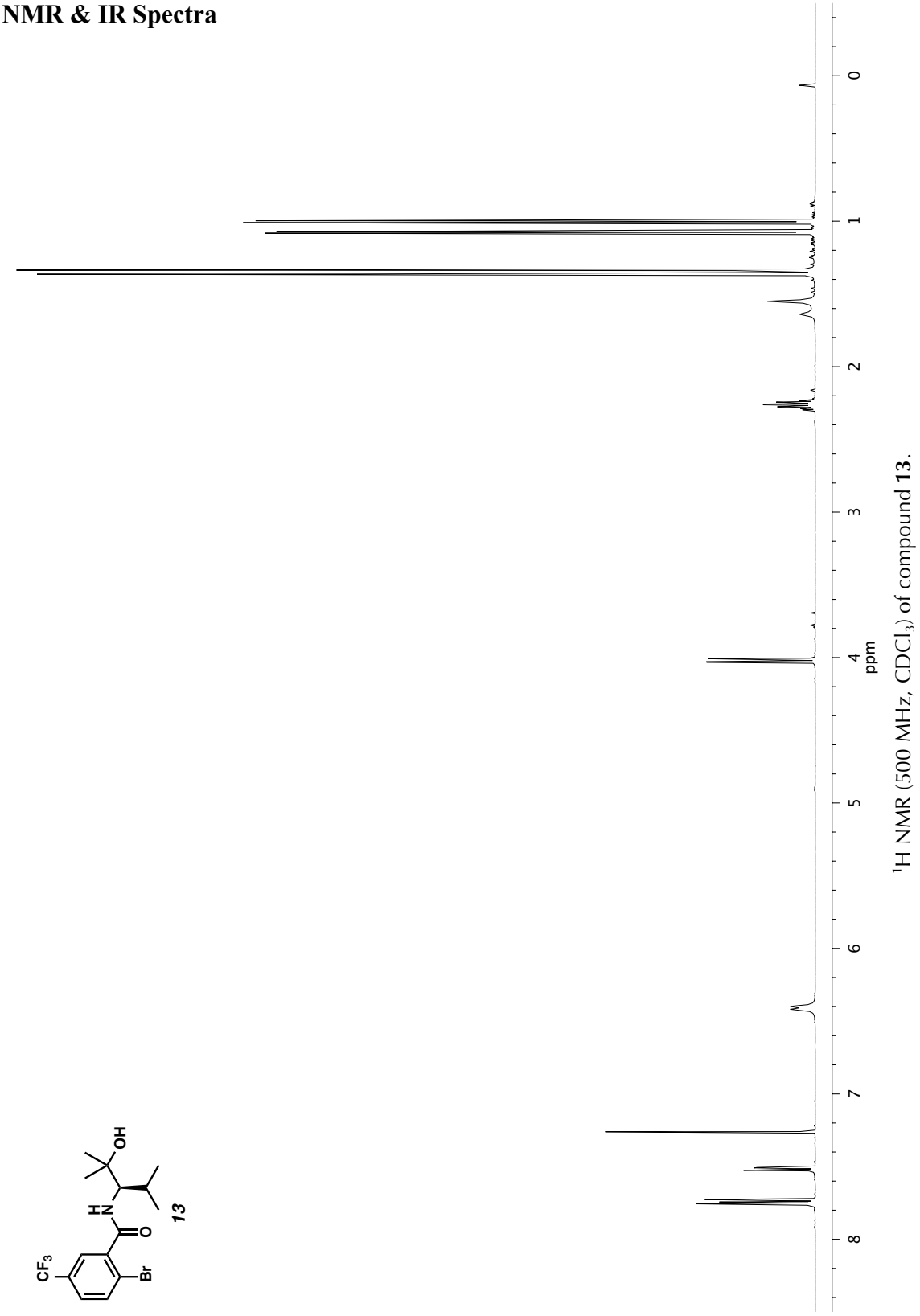
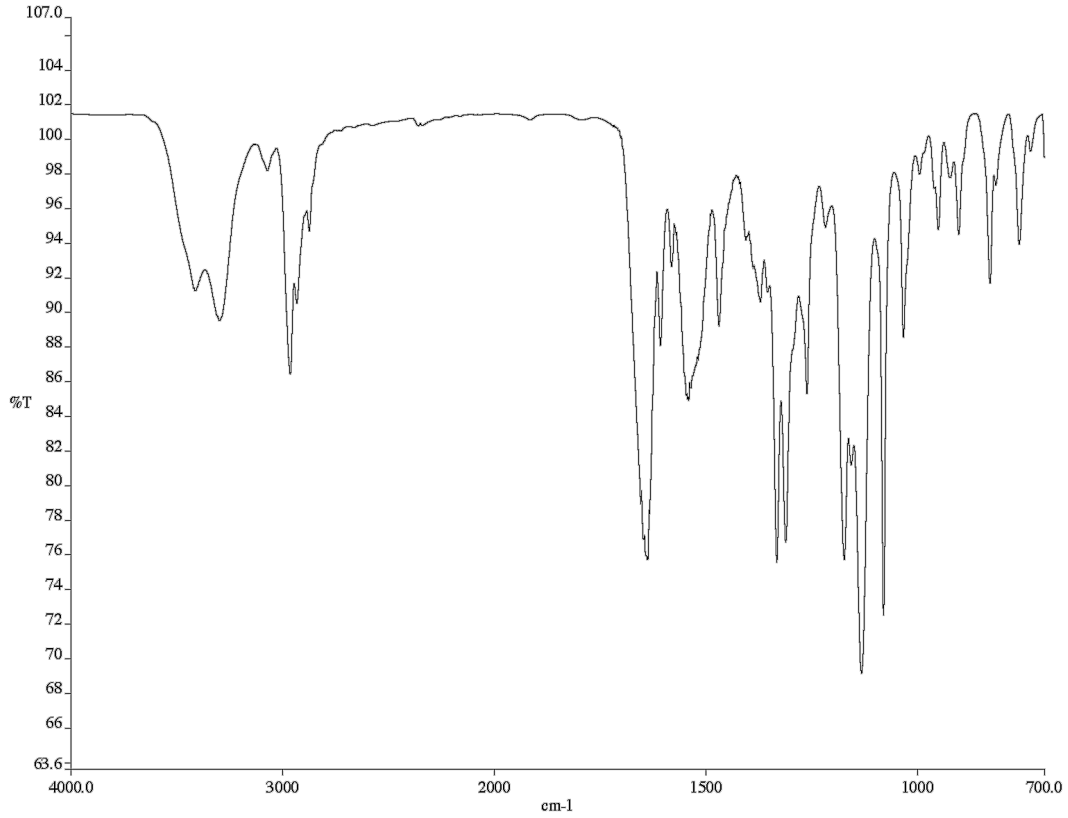
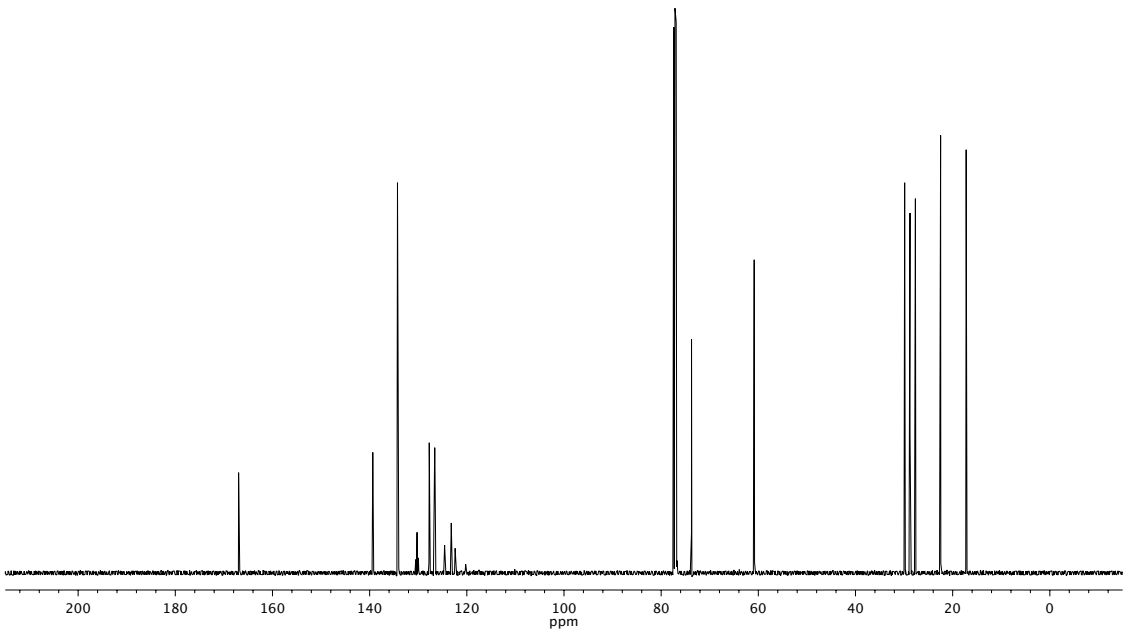
NMR & IR Spectra



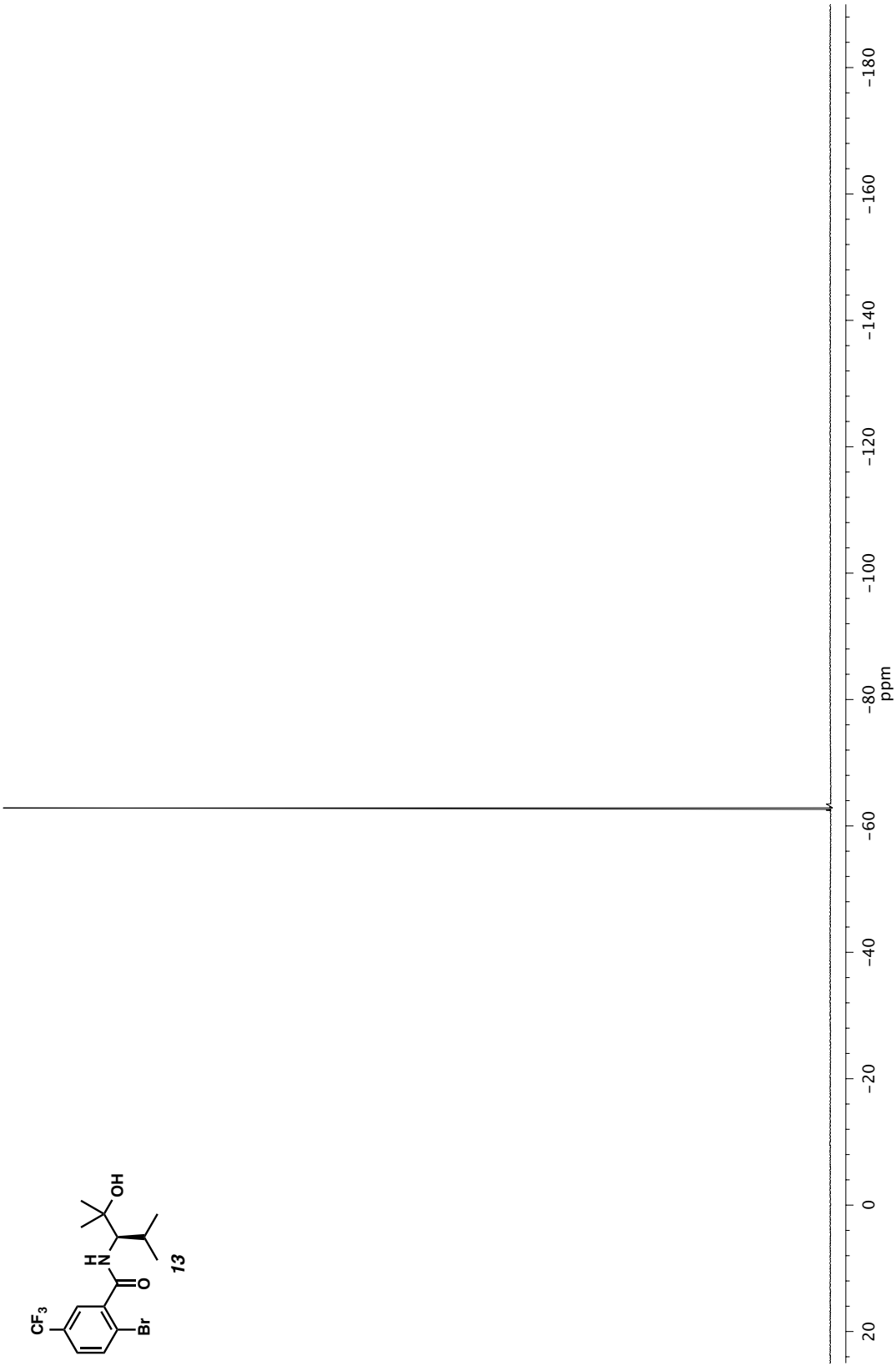
^{1}H NMR (500 MHz, $CDCl_3$) of compound **13**.



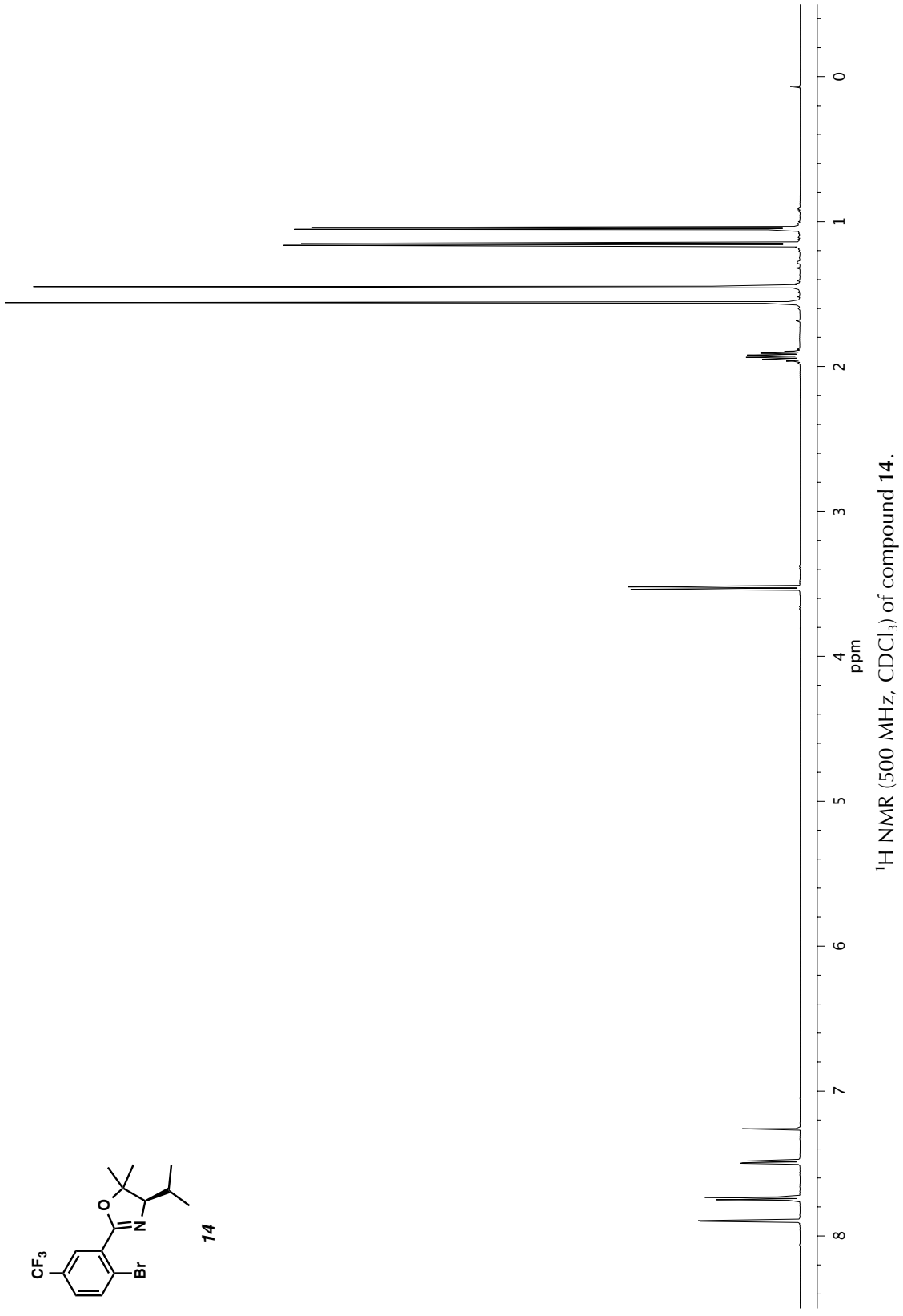
Infrared spectrum (Thin Film, NaCl) of compound **13**.



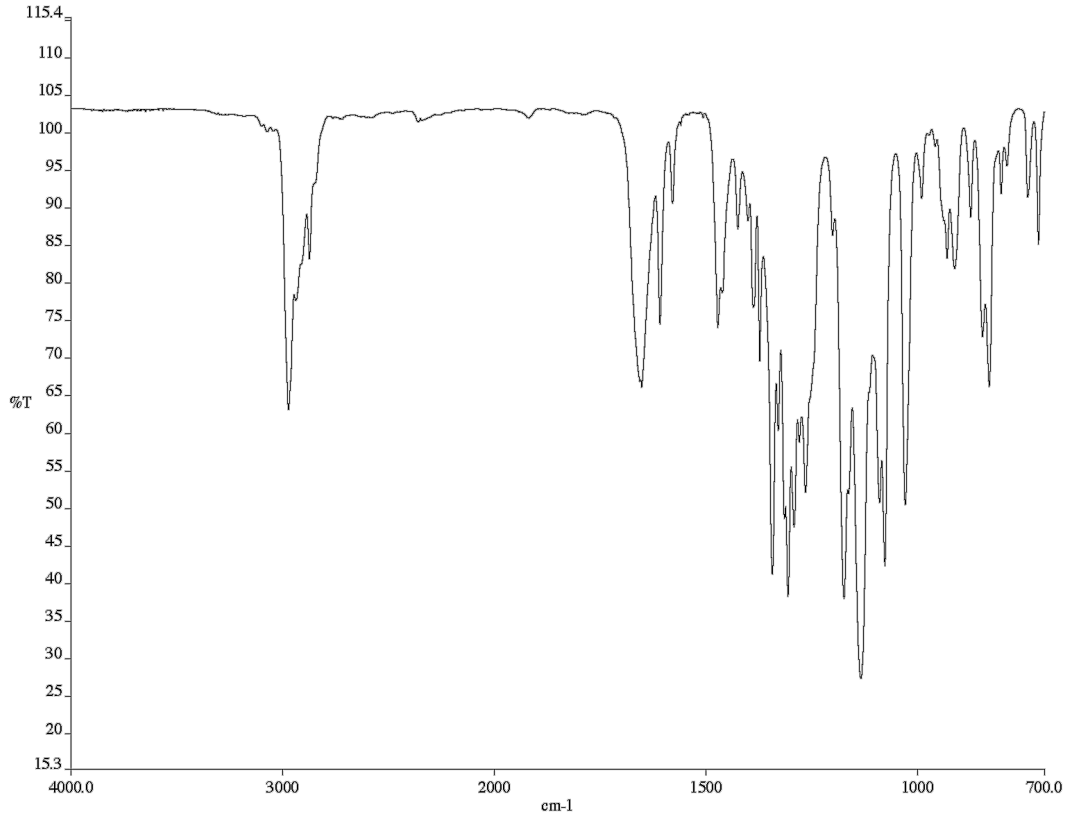
^{13}C NMR (126 MHz, $CDCl_3$) of compound **13**.



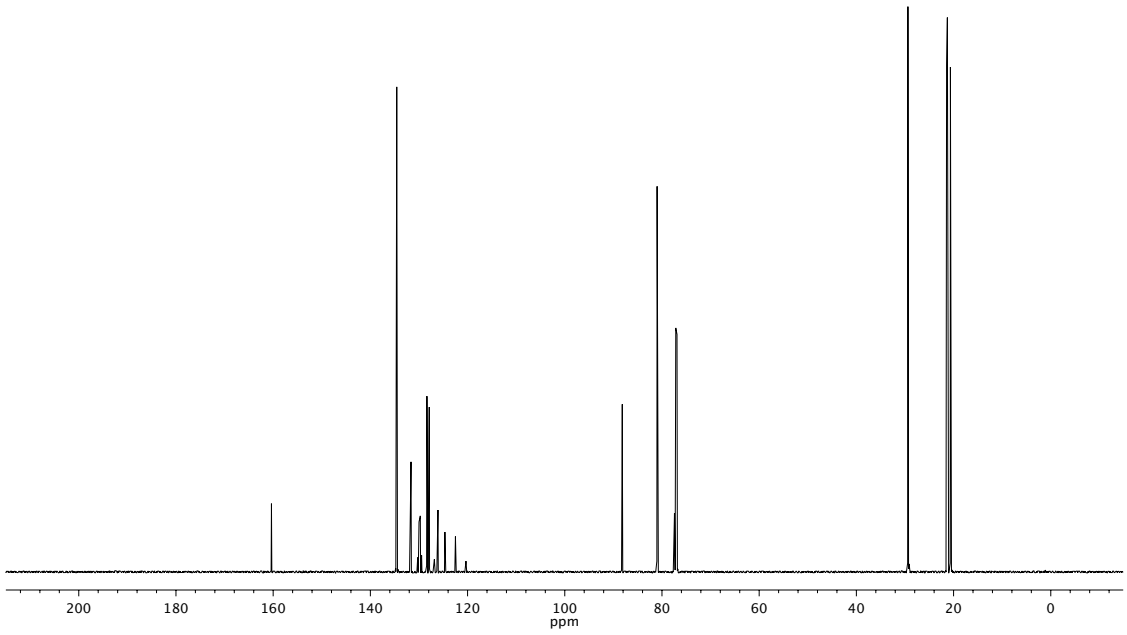
^{19}F NMR (282 MHz, $CDCl_3$) of compound **13**.



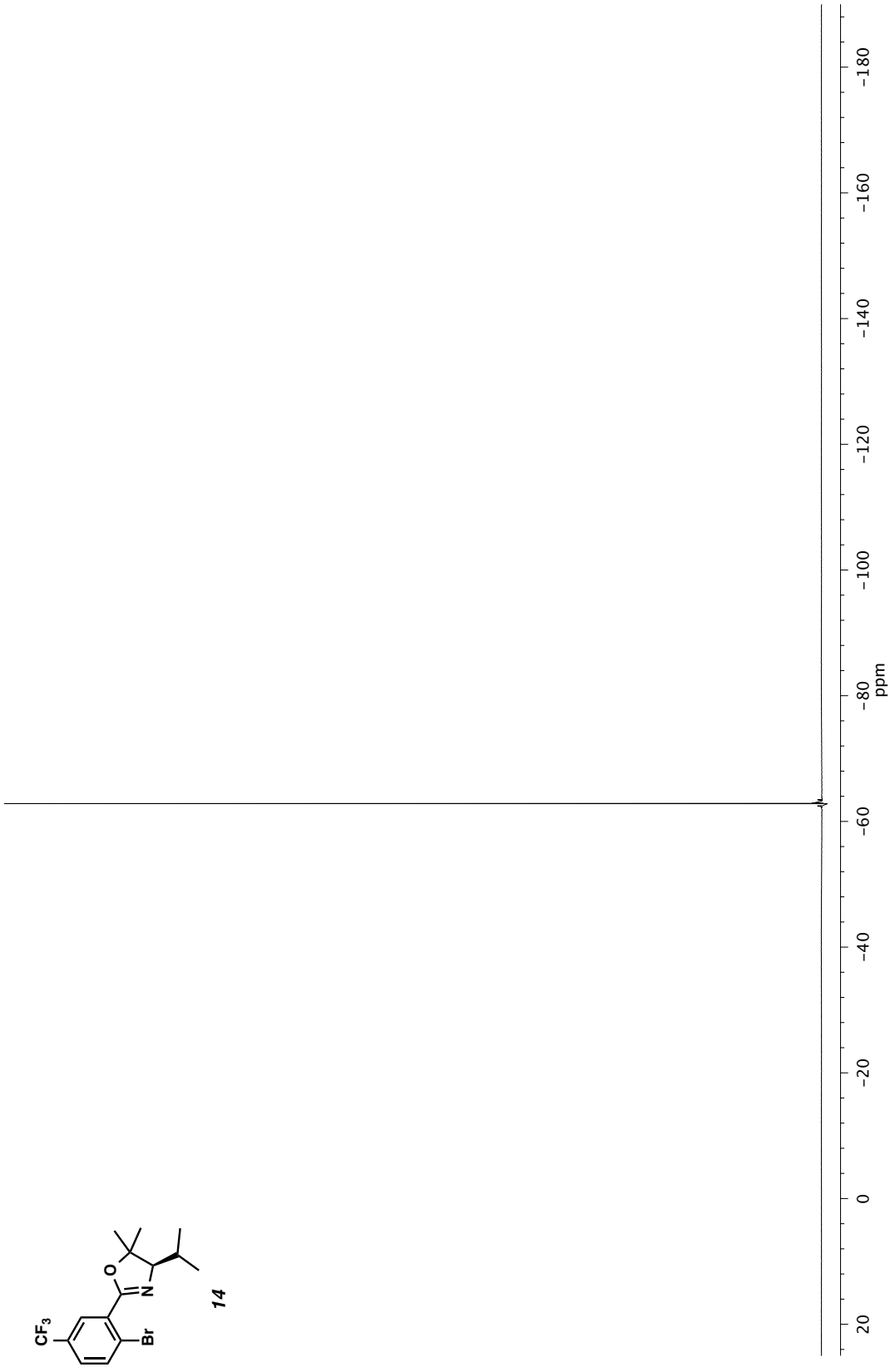
^{1}H NMR (500 MHz, $CDCl_3$) of compound **14**.



Infrared spectrum (Thin Film, NaCl) of compound **14**.

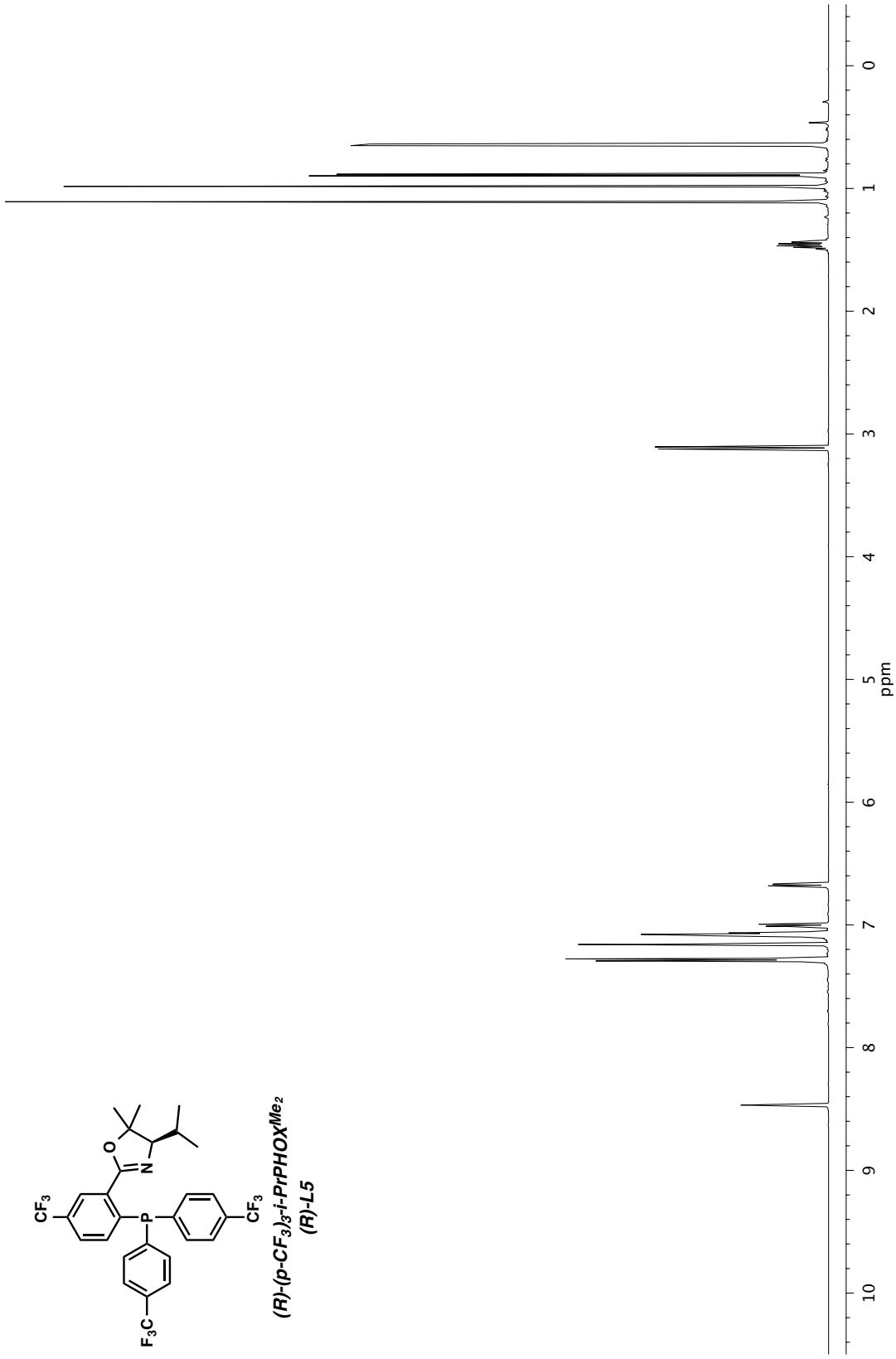


^{13}C NMR (126 MHz, $CDCl_3$) of compound **14**.



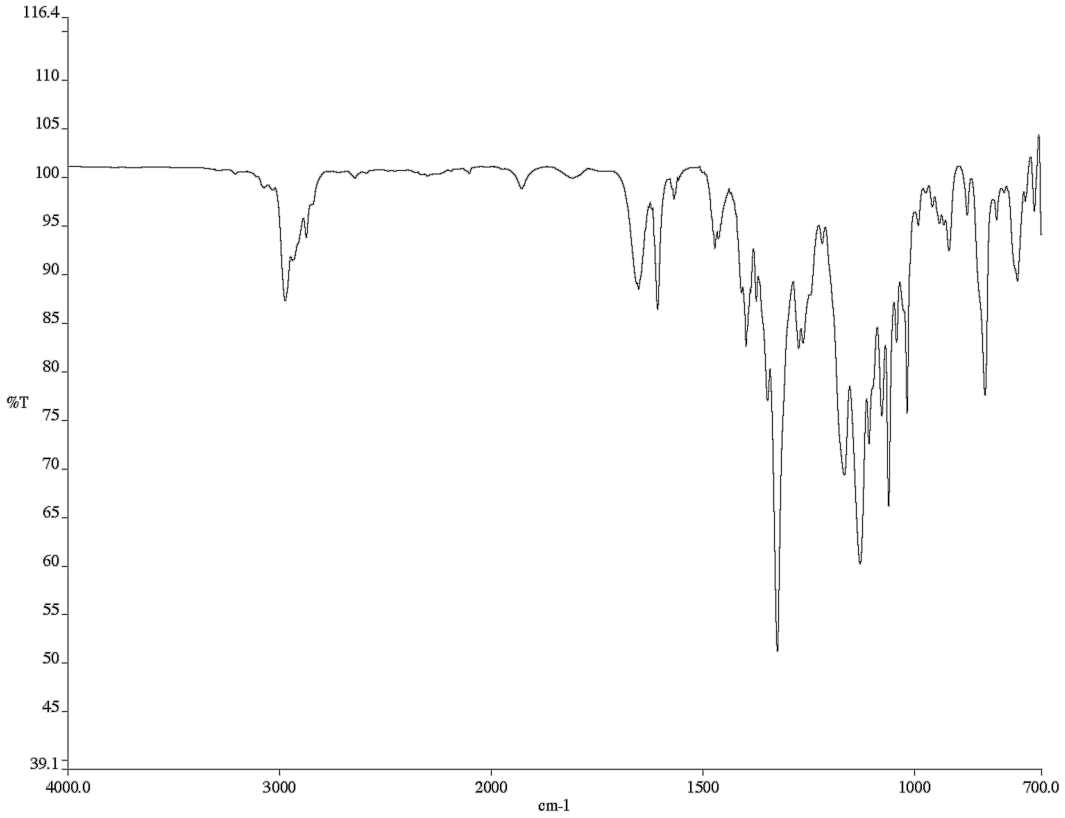
^{19}F NMR (282 MHz, $CDCl_3$) of compound **14**.

14

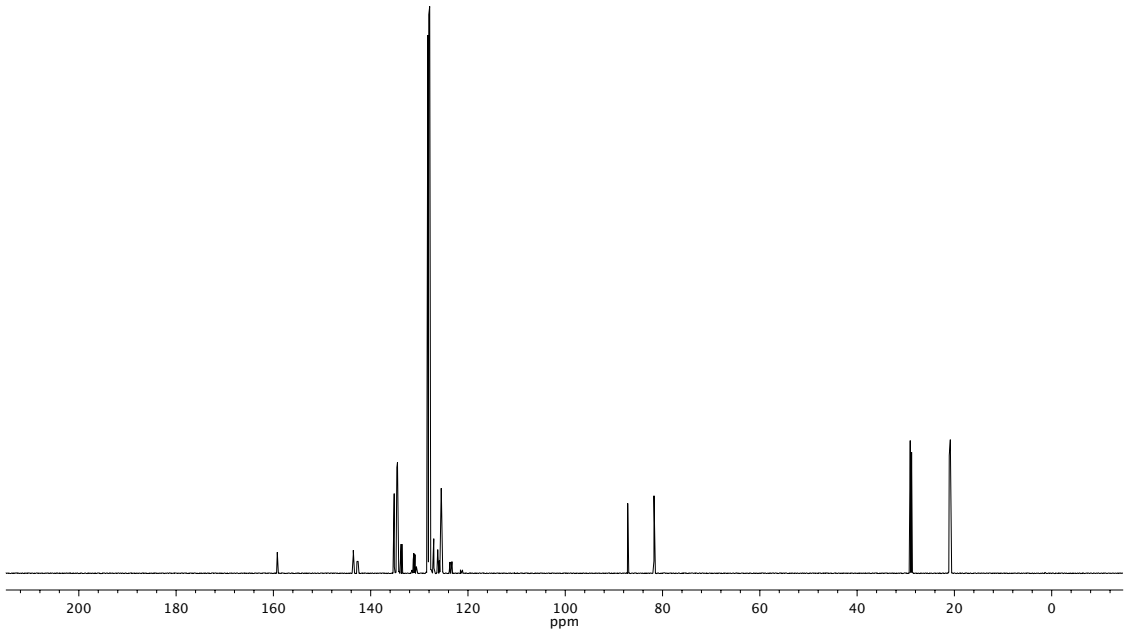


^{1}H NMR (500 MHz, C_6D_6) of compound ***(R)*-L5**.

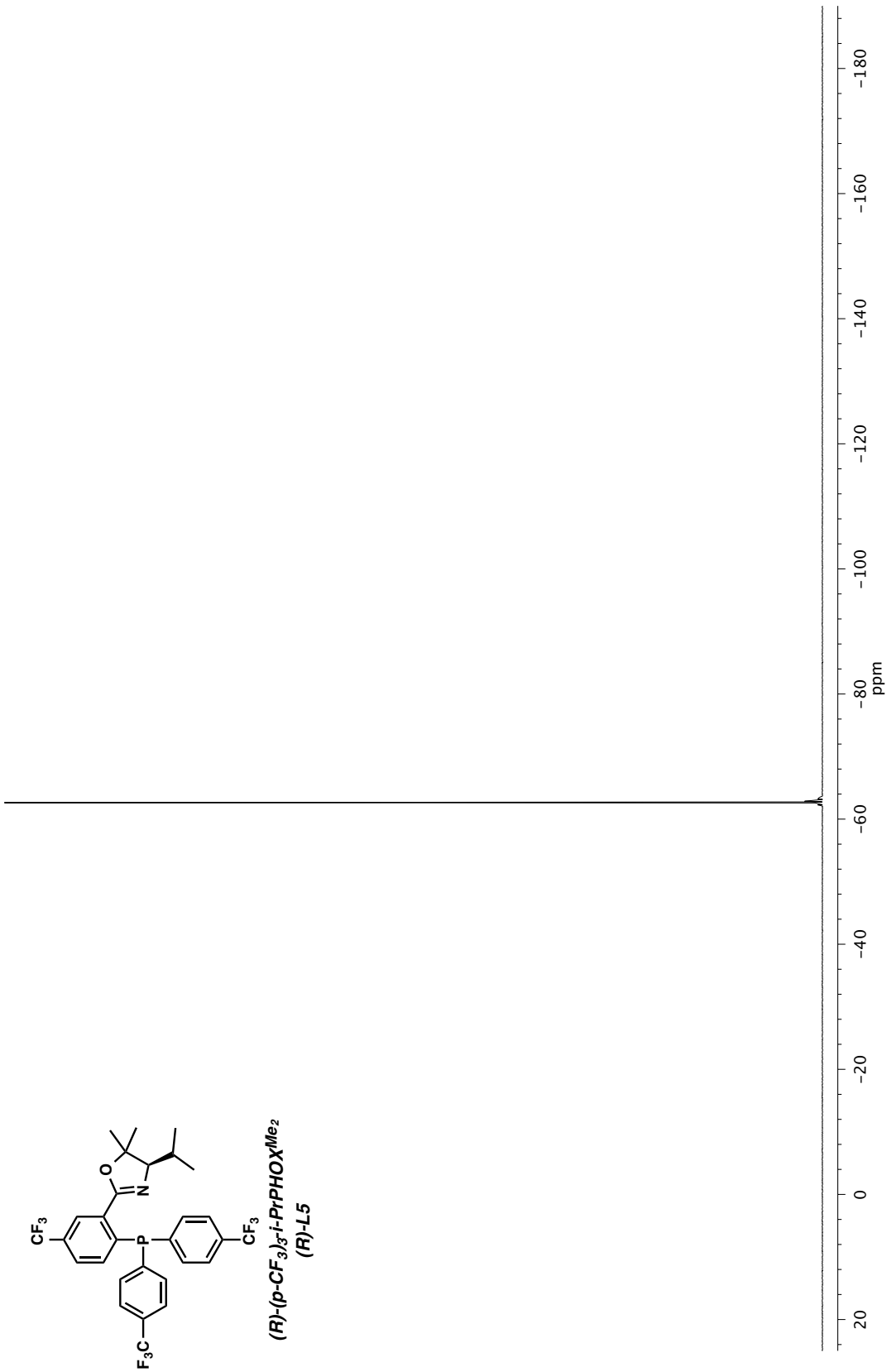
***(R)*-(*p*-CF_3)$_3$-*i*-PrPHOX^{Me_2}**
***(R)*-L5**



Infrared spectrum (Thin Film, NaCl) of compound **(*R*)-L5**.



^{13}C NMR (126 MHz, C_6D_6) of compound **(*R*)-L5**.



^{19}F NMR (282 MHz, C_6D_6) of compound ***(R)*-L5**.

***(R)*-(*p*-CF_3)$_3$-*i*-PrPHOX^{Me_2}**
***(R)*-L5**

^{31}P NMR (121 MHz, C_6D_6) of compound ***(R)*-L5**.