Development of Strong Brønsted Base Catalysis: Catalytic Direct-type Mannich Reactions of Non-activated Esters via a Product-base Mechanism

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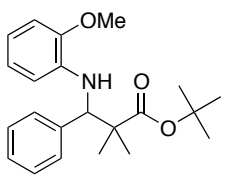
Electronic Supplementary Information

Contents:

General information: Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-ECA500, and JNM-ECX600 spectrometers in $CDCl_3$ unless otherwise noted. Tetramethylsilane (TMS) served as internal standard ($\delta = 0$) for ^{1}H NMR, and $CDCl_3$ served as internal standard ($\delta = 77.0$) for ^{13}C NMR. IR spectra were recorded with a JASCO FT/IR-4200 spectrometer. Column chromatography was conducted on Silica gel 60N (spherical, neutral, Kanto Chem. Co., Inc.). Potassium bis(trimethylsilyl)amide (KHMDS) was purchased from Aldrich Co., Ltd.. Potassium hydride (KH) was purchased from Kanto Chem. Co., Inc. as mineral oil dispersion and used after washing with anhydrous hexane and drying under reduced pressure inside a glove box fulfilled with dry argon gas. THF and TBME were distilled just before use in the presence of benzophenone and sodium. Imines **1** were prepared from *o*-anisidine and corresponding aldehyde in the presence of molecular sieves. Ester **2a** was prepared following the literature procedure.[1] Ester **2b** was prepared from propionic anhydride and *tert*-Butyl alcohol in a typical procedure.

General procedure: in a well-dried reaction tube, KH (0.10 mmol) was placed in a glove box fulfilled with Ar, and TBME (2.0 mL) was added. To the suspension, imine **1** (2.40 mmol, neat) and ester **2** (2.00 mmol, neat) were successively added at 20 ^{o}C, and the whole was stirred for 12 h at the same temperature. The reaction was quenched by adding water, and the mixture was extracted with diethyl ether (5 mL x 3). The organic layers were combined and dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the crude product obtained was purified by column chromatography on silica gel (hexane-diethyl ether) to afford the desired adduct **3**.

***tert*-Butyl 3-((2-methoxyphenyl)amino)-2,2-dimethyl-3-phenylpropanoate (3aa)**:



white solid; mp 64-68 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33-7.19 (m, 5 H), 6.71 (d, J = 8.2 Hz, 1 H), 6.64 (t, J = 7.6 Hz, 1 H), 6.54 (t, J = 7.6 Hz, 1 H), 6.28 (d, J = 7.6 Hz, 1 H), 5.36 (s, 1 H), 4.48 (s, 1 H), 3.86 (s, 3 H), 1.41 (s, 9 H), 1.22 (s, 3 H), 1.11 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.5, 146.6, 139.6, 137.1, 128.5, 127.8, 127.2, 121.1, 116.0, 110.4, 109.2, 80.9, 64.2, 55.4, 47.5, 27.8, 24.7, 20.3; IR(neat, cm^{-1})

3434, 1712, 1602, 1460, 1367, 1251, 1031; HRMS calcd for $C_{22}H_{29}NO_3$ $[M + H]^+$ 356.2226, found 356.2217.

***tert*-Butyl 3-(4-methoxyphenyl)-3-((2-methoxyphenyl)amino)-2,2-dimethyl-propanoate (3ba)**: yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, J = 8.5 Hz, 2 H),6.81-6.52 (m, 5 H), 6.29 (d, J = 7.4 Hz, 1 H), 5.34 (s, 1 H), 4.43 (s, 1 H), 3.84 (s, 3 H), 3.74 (s, 3 H), 1.41 (s, 9 H), 1.21 (s, 3 H), 1.10 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 158.7, 146.6, 137.0, 131.5, 129.4, 121.0, 115.9, 113.2, 110.4, 109.1, 80.7, 63.6, 55.3, 55.1, 47.5, 27.8, 24.6, 20.2; IR(neat, cm^{-1}) 3434, 1714, 1604, 1461, 1249, 1175, 1033; HRMS calcd for $C_{23}H_{31}NO_4$ $[M + H]^+$ 386.2331, found 386.2345.

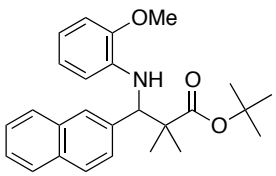
***tert*-Butyl 3-((2-methoxyphenyl)amino)-2,2-dimethyl-3-(*p*-tolyl)propanoate (3ca)**: yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21-7.17 (m, 2 H), 7.05 (d, J = 7.6 Hz, 2 H), 6.69-6.51 (m, 3 H), 6.29 (t, J = 7.6 Hz, 1 H), 5.32 (s, 1 H), 4.45 (s, 1 H), 3.82 (s, 3 H), 2.27 (s, 3 H), 1.40 (s, 9 H), 1.21 (s, 3 H), 1.10 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.4, 146.5, 137.1, 136.6, 136.4, 128.4, 128.3, 121.0, 115.8, 110.3, 109.1, 80.6, 63.8, 55.3, 47.4, 27.7, 24.7, 21.0, 20.2; IR(neat, cm^{-1}) 3434, 1716, 1602, 1459, 1368, 1251, 1227, 1031; HRMS calcd for $C_{23}H_{31}NO_3$ $[M + H]^+$ 370.2382, found 370.2350.

***tert*-Butyl 3-(4-chlorophenyl)-3-((2-methoxyphenyl)amino)-2,2-dimethylpropanoate (3da)**: yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.19 (m, 4 H), 6.69-6.52 (m, 3 H), 6.24 (d, J = 7.9 Hz, 1 H), 5.36 (s, 1 H), 4.45 (s, 1 H), 3.79 (s, 3 H), 1.39 (s, 9 H), 1.21 (s, 3 H), 1.08 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8, 146.4, 138.1, 136.6, 132.7, 129.6, 127.8, 120.8, 116.1, 110.2, 109.0, 80.8, 63.5, 55.1, 47.1, 27.6, 24.5, 20.2; IR(neat, cm^{-1}) 3432, 1718, 1602, 1459, 1368, 1251, 1227, 1031; HRMS calcd for $C_{22}H_{28}ClNO_3$ $[M + H]^+$ 390.1836, found 390.1821.

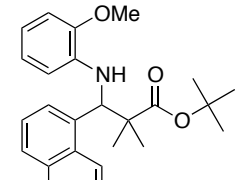
***tert*-Butyl 3-((2-methoxyphenyl)amino)-2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)- propanoate (3ea)**: yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54-7.46 (m, 4 H), 6.74-6.57 (m, 3 H), 6.24 (d, J = 7.6 Hz, 1 H), 5.60 (s, 1 H), 4.54 (s, 1 H), 3.86 (s, 3 H), 1.42 (s, 9 H), 1.24 (s, 3 H), 1.12 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.9, 146.7, 143.9, 136.4, 129.9, 129.5 (q, ^2J = 32.8 Hz),

128.8, 124.8 (q, ^{3}J = 3.9 Hz), 124.1 (q, ^{1}J = 275.3 Hz), 121.0, 116.7, 110.5, 109.3, 81.2, 64.1, 55.3, 47.3, 27.8, 24.6, 20.5; IR(neat, cm^{-1}) 3433, 1718, 1602, 1460, 1326, 1252, 1227, 1167, 1068; HRMS calcd for $C_{23}H_{28}F_3NO_3$ $[M + H]^+$ 424.2100, found 424.2093.

***tert*-Butyl 3-((2-methoxyphenyl)amino)-2,2-dimethyl-3-(naphthalen-2-yl)-propanoate (3fa)**: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80-7.74 (m, 4 H), 7.48-7.40 (m, 3 H), 6.72-6.50 (m, 3 H), 6.32 (d, J = 7.9 Hz, 1 H), 5.45 (s, 1 H), 4.65 (s, 1 H), 3.88 (s, 3 H), 1.42 (s, 9 H), 1.27 (s, 3 H), 1.16 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 146.6, 137.4, 137.1, 133.0, 132.9, 127.9, 127.5, 127.5, 127.4, 126.5, 125.8, 125.6, 121.0, 116.0, 110.5, 109.2, 80.9, 64.4, 54.4, 47.7, 27.8, 24.8, 20.5; IR(neat, cm^{-1}) 3434, 1715, 1601, 1460, 1369, 1250, 1226, 1031; HRMS calcd for $C_{26}H_{31}NO_3$ $[M + H]^+$ 406.2382, found 406,2365.

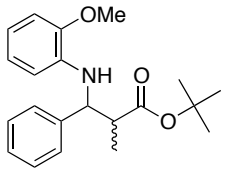


***tert*-Butyl 3-((2-methoxyphenyl)amino)-2,2-dimethyl-3-(naphthalen-1-yl)-propanoate (3ga)**: yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, J = 9.1 Hz, 1 H), 7.85-7.34 (m, 6 H), 6.68-6.16 (m, 4 H), 5.62 (s, 1 H), 5.53 (s, 1 H), 3.84 (s, 3 H), 1.44 (s, 9 H), 1.19 (s, 3 H), 1.15 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 146.5, 137.0, 135.9 133.5, 132.7, 129.1, 127.8 125.8, 125.7, 125.2, 125.1, 123.2, 121.1, 115.9, 110.1, 109.1, 80.9, 64.4, 55.3, 48.7, 27.8, 25.5, 20.2; IR(neat, cm^{-1}) 3435, 1716, 1601, 1459, 1391, 1369, 120, 1226, 1031; HRMS calcd for $C_{26}H_{31}NO_3$ $[M + H]^+$ 406.2382, found 406,2373.



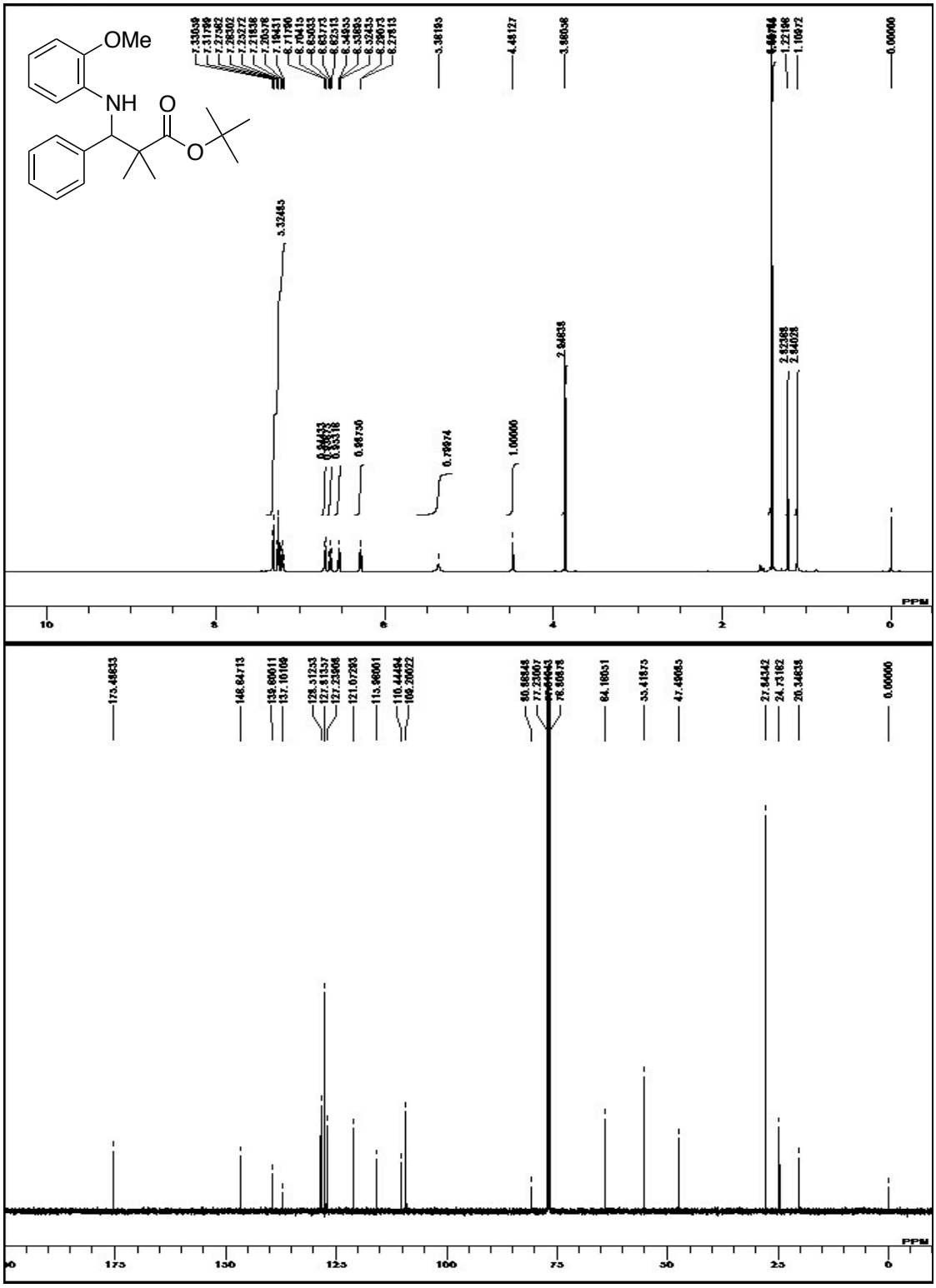
***tert*-Butyl 3-(furan-2-yl)-3-((2-methoxyphenyl)amino)-2,2-dimethylpropanoate (3ha)**: yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.19 (s, 1H), 6.69-6.63 (m, 2 H), 6.54-6.44 (m, 2 H), 6.14 (t, J = 2.4 Hz, 1 H), 6.07 (t, J = 2.4 Hz, 1 H), 5.04 (s, 1 H), 4.58 (s, 1 H), 3.72 (s, 3H), 1.33(s, 9H), 1.17 (s, 3 H), 1.13 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.0, 154.0, 146.8, 141.4, 137.1, 121.0, 116.6, 110.4, 110.0, 109.5, 107.6, 80.6, 58.1, 55.3, 47.5, 27.7, 23.6, 21.1; IR(neat, cm^{-1}) 3433, 1720, 1601, 1460, 1368, 1250, 1228, 1031; HRMS calcd for $C_{20}H_{27}NO_4$ $[M + H]^+$ 346.2018, found 346.2020.

tert*-Butyl 3-((2-methoxyphenyl)amino)-2-methyl-3-phenylpropanoate (3ab, *syn*/*anti* 37:63)[2]**: colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$): ***anti: δ 7.33-7.19 (m, 5 H), 6.74-6.54 (m, 3 H), 6.35 (d, J = 6.9 Hz, 1 H), 5.34 (s, 1 H), 4.41 (d, J = 6.9 Hz 1 H), 3.86 (s, 3 H), 2.76-2.72 (m, 1 H), 1.39 (s, 9 H), 1.10 (d, J = 6.9 Hz, 3 H): ***syn***: δ

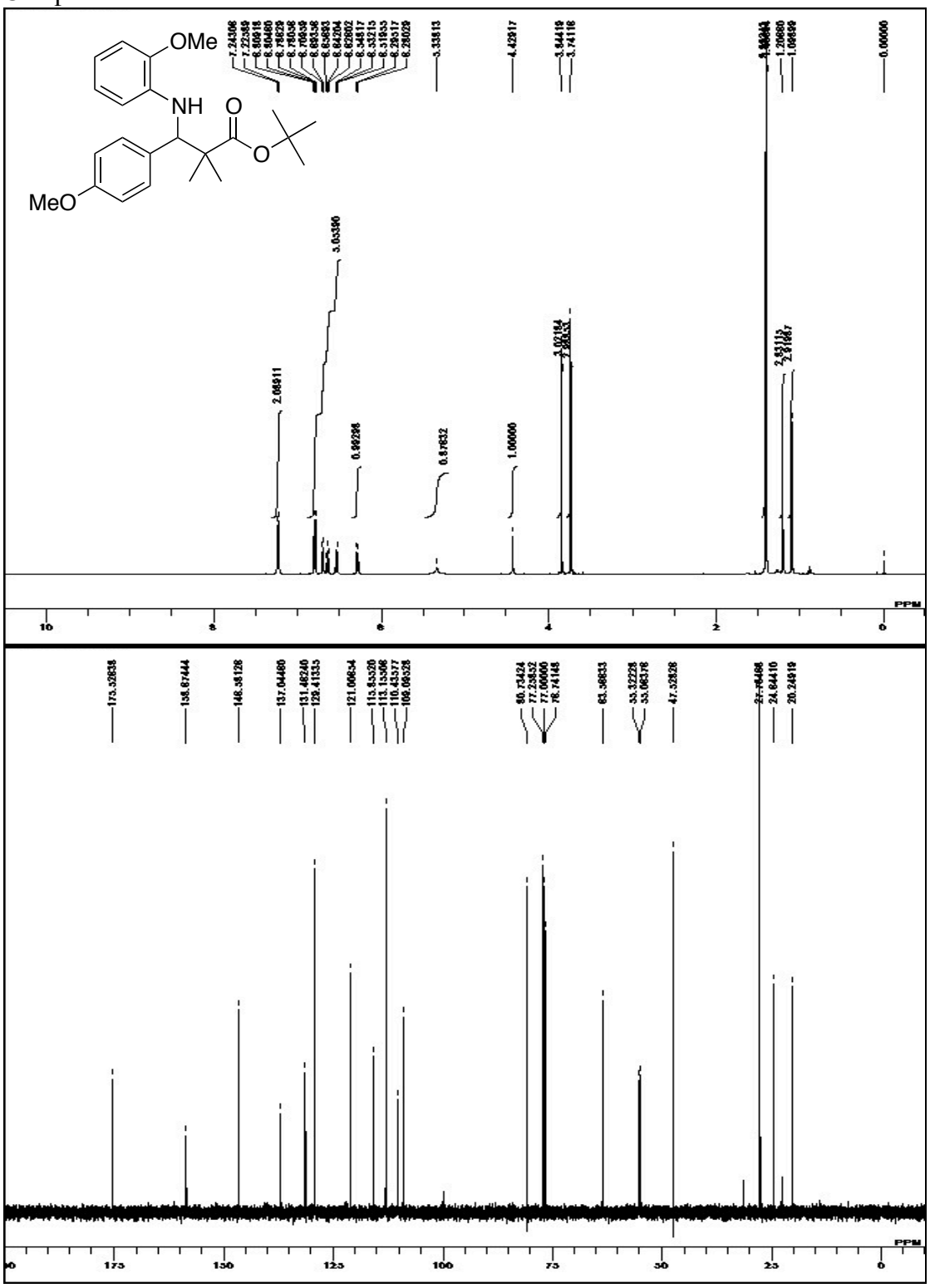


7.33-7.19 (m, 5 H), 6.74-6.54 (m, 3 H), 6.34 (d, J = 7.6 Hz, 1 H), 5.08 (s, 1 H), 4.65 (d, J = 4.8 Hz 1H), 3.86 (s, 3 H), 2.91-2.86 (m, 1 H), 1.34 (s, 9 H), 1.15 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$): ***anti***: δ 173.1, 146.6, 141.5, 136.9, 128.3, 127.1, 127.0, 121.1, 116.0, 110.9, 109.3, 80.8, 60.6, 55.4, 47.8, 27.9, 15.1: ***syn***: δ 174.0, 146.7, 141.0, 137.1, 128.2, 127.2, 127.0, 121.1, 116.3, 110.5, 109.3, 80.9, 59.8, 55.4, 47.2, 27.8, 12.5; IR(neat, cm^{-1}) 3425, 2977, 2936, 1727, 1602, 1517, 1457, 1365, 1247, 1224, 1153, 1029; HRMS calcd for $C_{21}H_{27}NO_3$ $[M + H]^+$ 342.2069, found 342.2060.

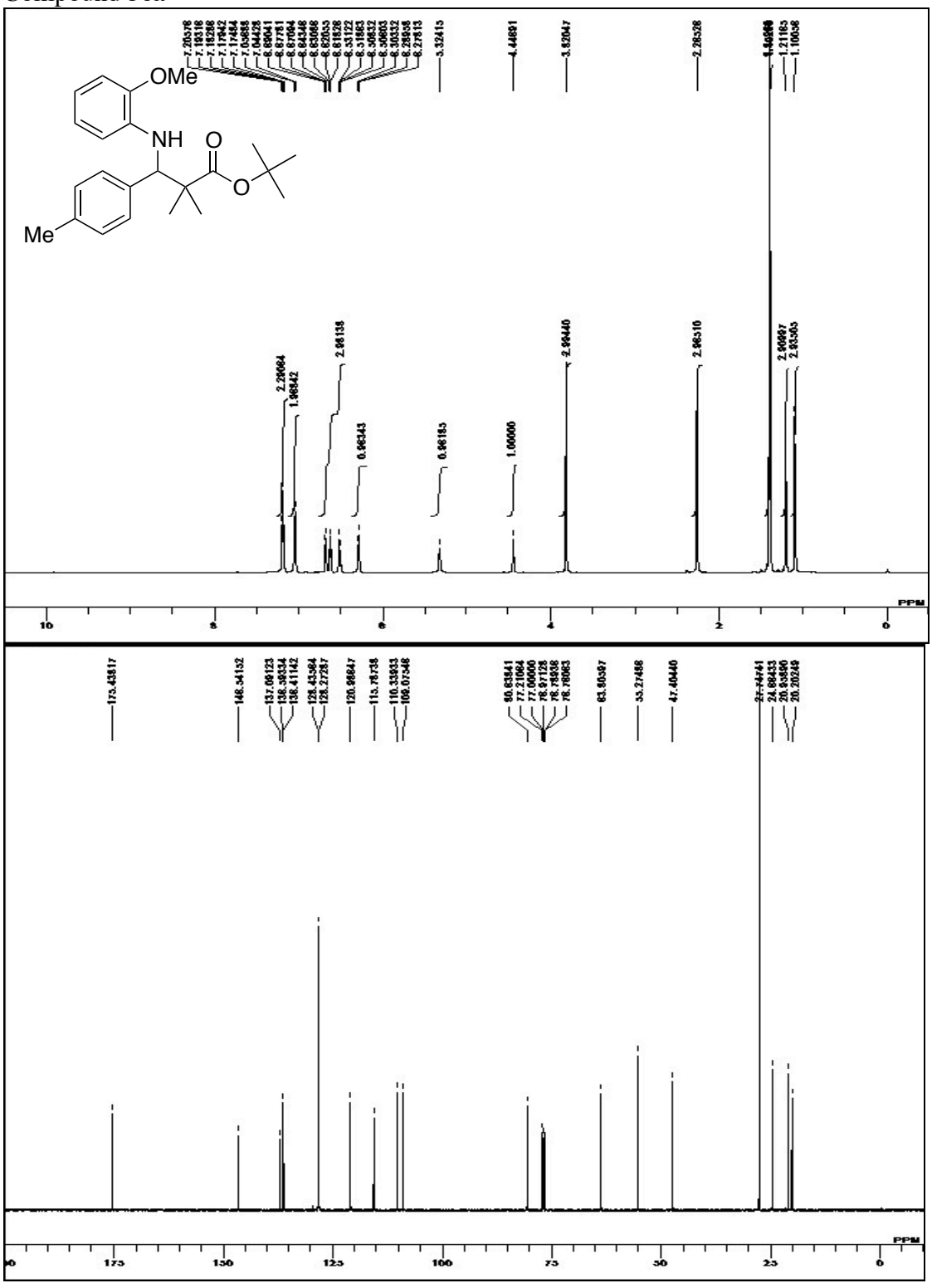
Compound
3aa



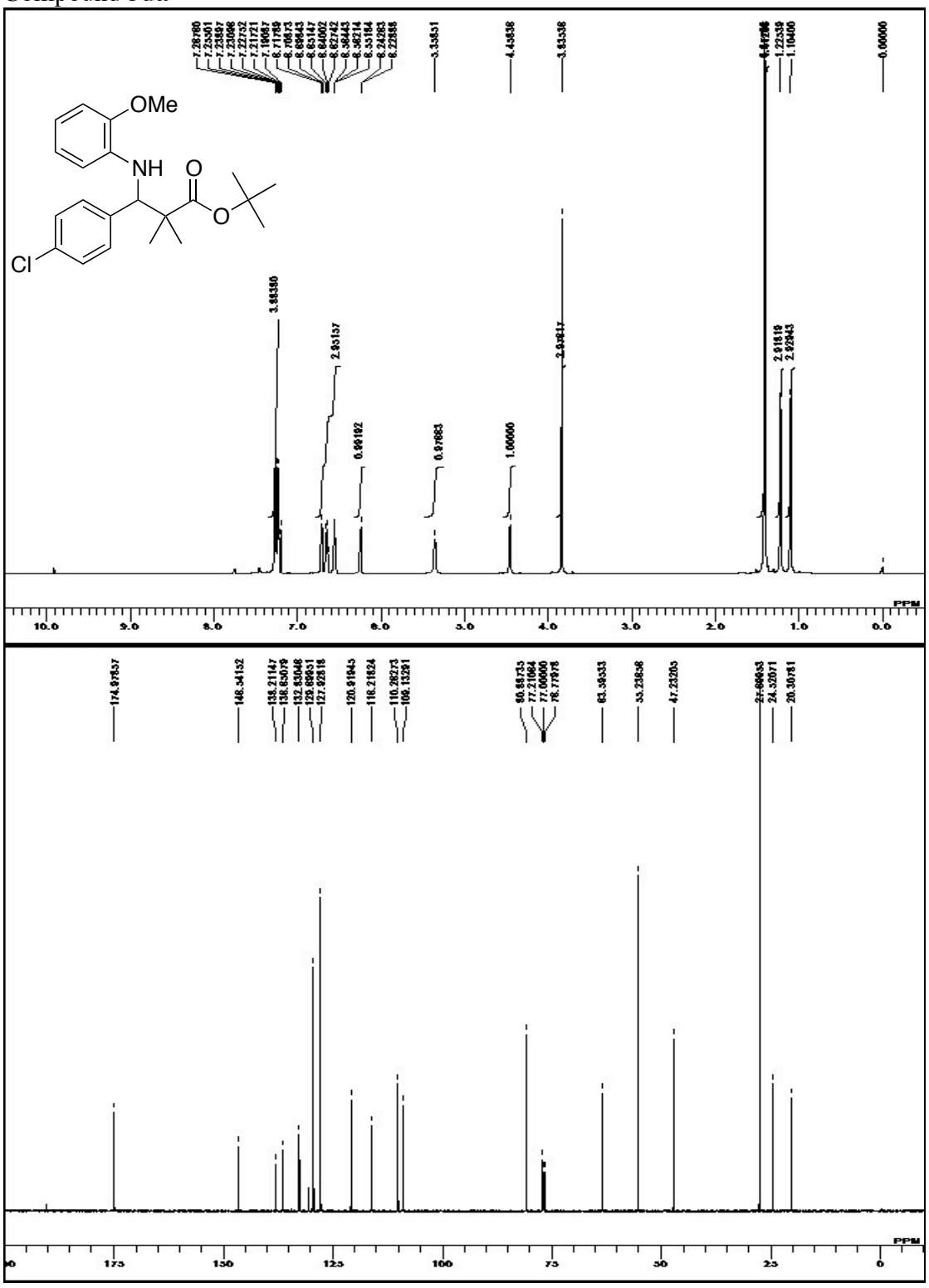
Compound **3ba**



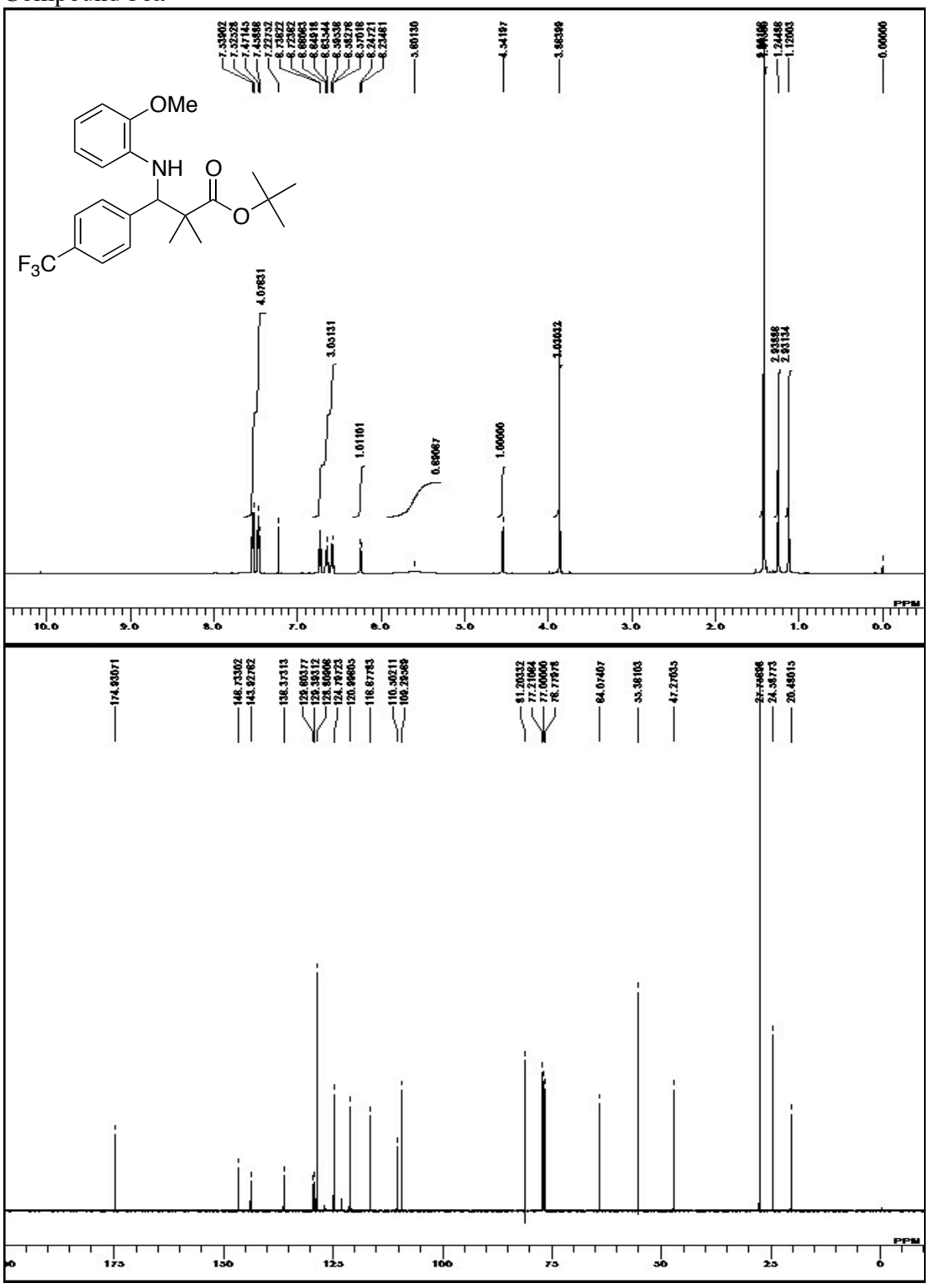
Compound **3ca**



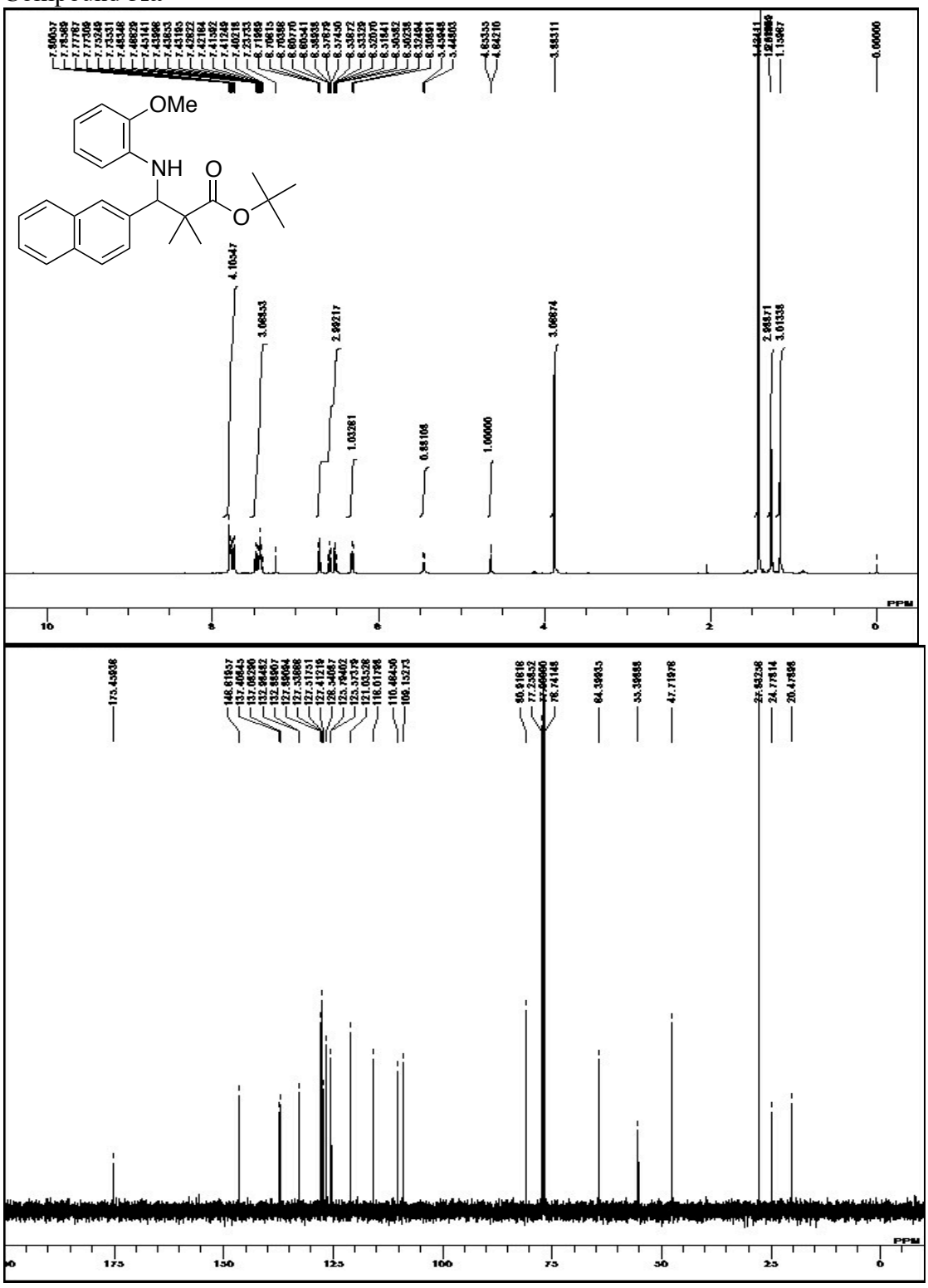
Compound **3da**



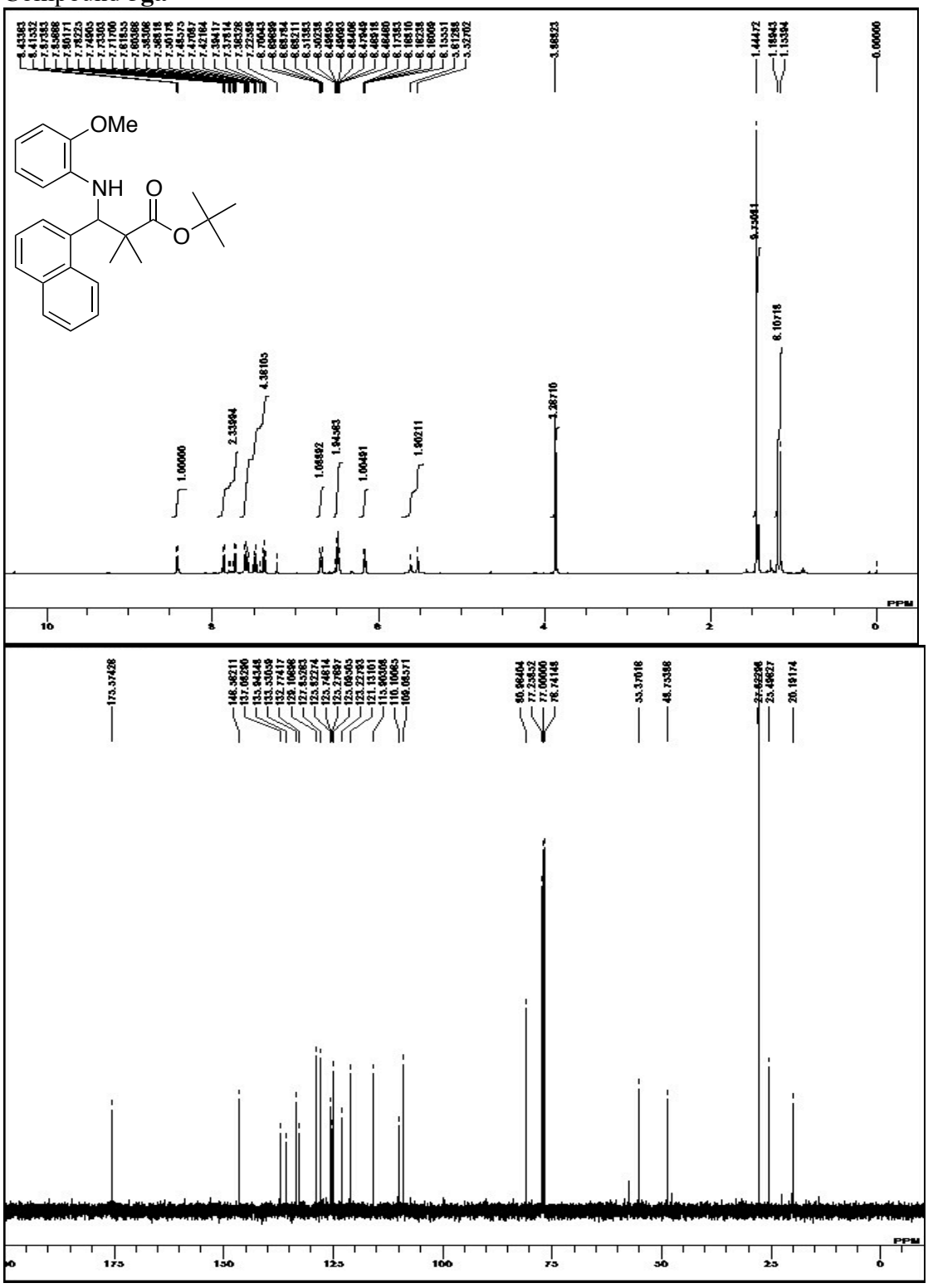
Compound **3ea**



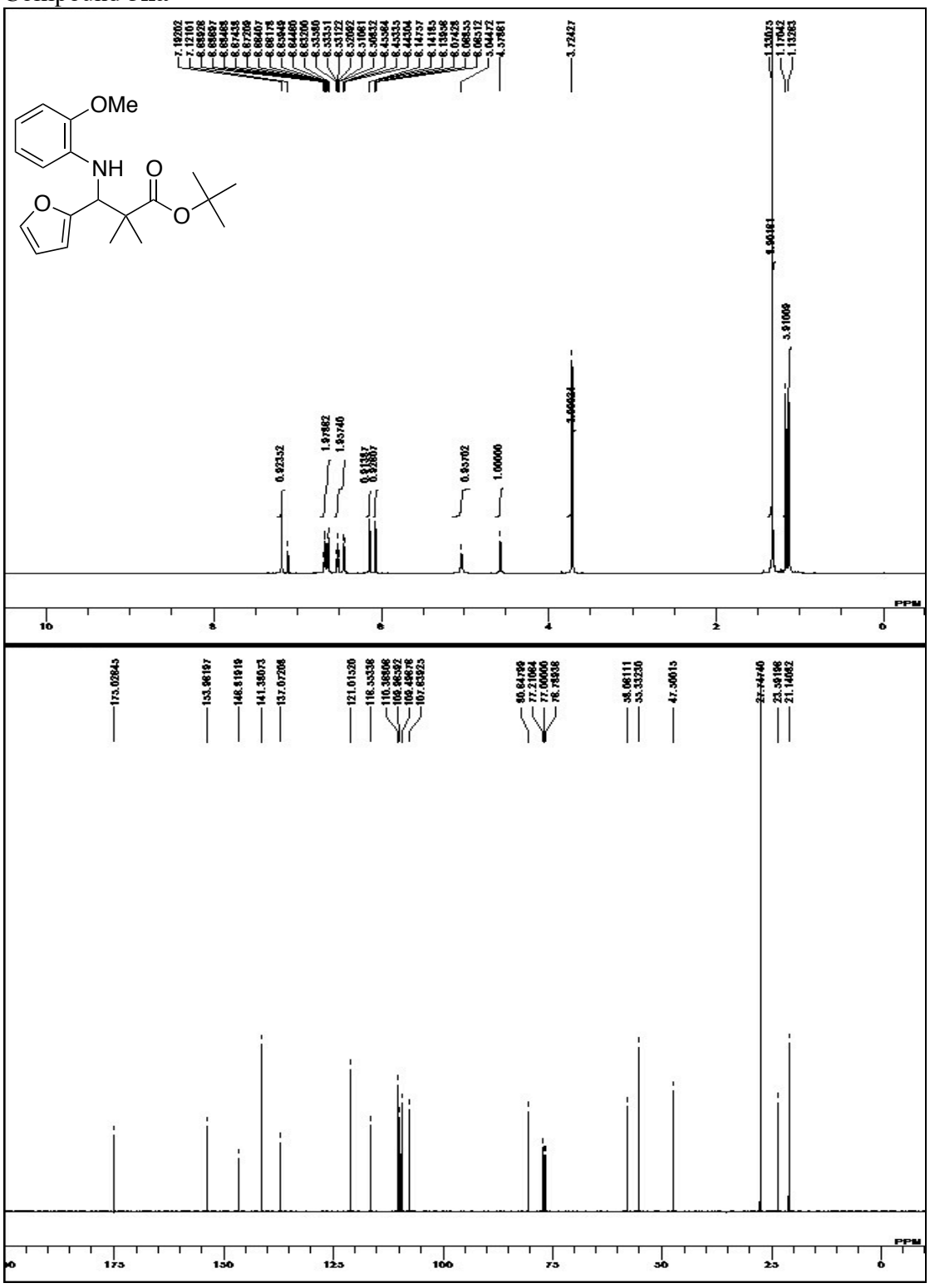
Compound **3fa**



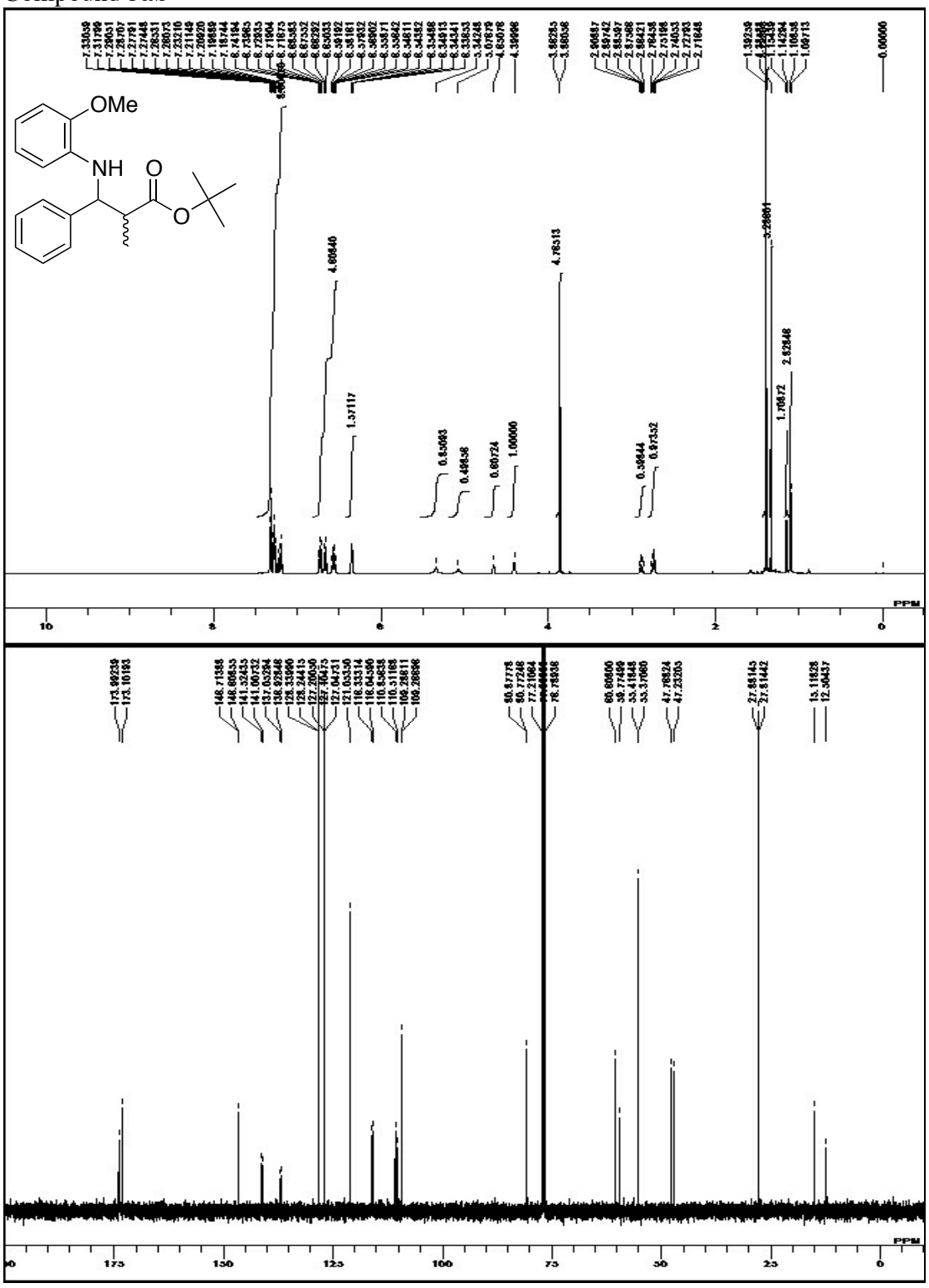
Compound **3ga**



Compound **3ha**



Compound **3ab**



References:

(1) Renaudat, A.; Jean-Gérard, L.; Jazzar, R.; Kefalidis, C. E., Clot, E.; Baudoin, O. *Angew. Chem. Int. Ed.* **2010**, *49*, 7261.

(2) Relative configuration of the diastereomers were determined by comparison with ^{13}C NMR chemical shifts of the related compounds; see Kobayashi, S.; Kobayashi, J.; Ishitani, H.; Ueno, M. *Chem. Eur. J.* **2002**, *8*, 4185.