COMPLETE *N*-1 REGIOCONTROL IN THE FORMATION OF *N*-ARYL IMIDAZOLES. SYNTHESIS OF THE ACTIVE SITE HIS-TYR SIDE CHAIN COUPLED DIPEPTIDE OF CYTOCHROME *C* OXIDASE♦

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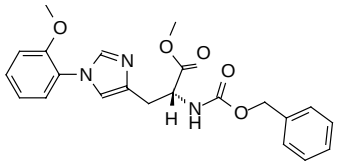
SUPPORTING INFORMATION

General. Solvents for extractions and chromatography were technical grade and used without any further purification (light petroleum ether, ether, ethyl acetate, hexane). Reaction solvents were used as received (CH_2Cl_2, $CHCl_3$). *p*-Methoxyphenyllead triacetate was made from direct plumbation of anisole and lead tetraacetate and used over a two-week period.[1] Other lead reagents were prepared form the corresponding tin compound.[2]

General procedure for arylations:

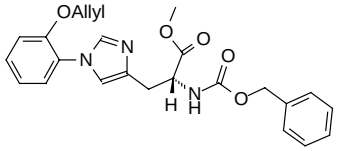
Amine (1 mmol) is stirred in 10 mls. of methylene chloride at room temperature. To this heterogeneous solution, copper (II) acetate (0.1 mmol) is added along with aryllead tricarboxylate (1.4 mmol). The blue solution turns homogenous after five minutes of stirring. Upon completion (3-14 hours), the reaction is quench with 3 ml of a water-sodium sulfide and stirred for an addition 5 minutes. The reaction turns black with some precipitate. The reaction mixture is passed through Celite. Then the solution is extracted with methylene chloride (3 x 5 ml). The organic layer is dried over sodium sulfate, and concentrated *in-vacuo*.



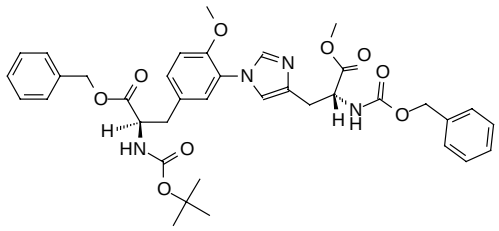
Reaction of (**5** + **6**) **1-*o*-methoxyphenyl(CBZ)histidinemethylester**
Clear oil. $[\alpha]_D$= -30. (*c* 0.4, MeOH)
^{1}H NMR (500 MHz, $CDCl_3$) 7.668 (s, 1H), 7.374-7.212 (m, 7H), 7.040-7.003 (m, 2H), 6.955 (s, 1H), 6.307 (d, *J* = 8 Hz, 1H), 5.130 (q, *J* = 5.5Hz, 1H), 4.675-4.649 (m, 1H), 3.821, (s, 3H), 3.727 (s, 3H), 3.191 (dq, *J* = 32, 5.5, Hz, 2H).

[1] Kozyrod, R.P.; Pinhey, J.T. *Org. Synth.***1984**, *62*, 24.
[2] Kozyrod, R. P.; Morgan, J.; Pinhey, J. T. *Aust. J. Chem*. **1985**, *38*, 1147-1153.

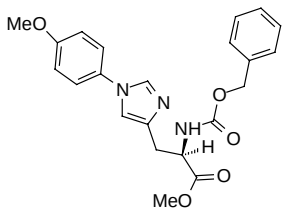
^{13}C(125 Hz, $CDCl_3$) 172.2, 156.1, 152.4, 137.5, 136.7, 136.5, 128.9, 128.4, 128.0, 128.0, 126.3, 125.3, 121.0, 117.9, 112.3, 66.8, 55.8, 54.0, 52.2, 30.0 Hz.
IR (neat) 3334, 2951, 1720, 1512, 1266 cm^{-1}.
Anal. Calcd. for $C_{22}H_{23}N_3O_5$: C, 64.54; H, 5.66; N, 10.26; Found: C, 64.37; H, 6.00; N, 10.12.



Reaction of (**7** + **6**): clear oil, $[\alpha]_D$= 5.0 (*c* 0.4, MeOH)
^{1}H NMR (500 MHz, $CDCl_3$) 7.694 (s,1H), 7.370-7.229 (m, 8H), 7.215 (d, 1H, *J* = 1.5Hz), 7.033-6.985 (m, 3H), 6.379 (d, *J* = 3 Hz, 1H), 5.974-5.919 (m, 1H), 5.323 (d, *J* = 17Hz, 1H), 5.243 (d, *J* = 11Hz, 1H), 5.151-5.094 (m, 2H), 4.691-4.655 (m, 1H), 4.545 (d, *J* = 5.5 Hz, 2H), 3.714 (s, 3H), 3.224 (dq, *J* = 26.5, 15, 5.5 Hz, 2H).
^{13}C(125 Hz, $CDCl_3$) 172.3, 156.3, 151.5, 137.7, 136.8, 136.7, 132.4, 128.9, 128.5, 128.2, 128.1, 126.8, 125.5, 121.4, 118.0, 114.0, 69.6, 66.9, 54.1, 52.4, 30.2.
IR (neat) 3343, 2952, 2251, 1721, 1510 cm^{-1}.
ESIHRMS (M^+ + H) *m / z* 436.1840 ($C_{24}H_{25}N_3O_5$ requires 436.1867).

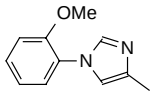


Reaction of (**8** + **6**) clear hard gum, $[\alpha]_D$= 10.0 (*c* 1.5, MeOH)
^{1}H NMR (500 MHz, $CDCl_3$) 7.606 (s, 1H), 7.377-7.267 (m, 7H), 7.005 (d, *J* = 8 Hz.), 6.927-6.857 (m, 3H), 6.333 (d, *J* = 8 Hz., 1H), 5.193-5.013 (m,), 4.674-4.606 (m,), 3.785 (s,3H), 3.726 (s, 3H), 3.208-3.014(m,), 1.406(s, 9H).
^{13}C(125 Hz, $CDCl_3$) 172.3, 171.6, 156.2, 151.4, 137.6, 136.7,136.6, 135.1, 129.7, 128.9, 128.7, 128.6, 128.5, 128.3, 128.2, 128.1, 126.4, 118.0, 112.5, 94.9, 80.3, 67.3, 66.9, 55.9, 54.5, 54.2, 52.7, 37.4, 30.1, 29.8, 28.4 Hz.
IR (neat) 3350, 2976, 1714, 1519, 1256, 1169 cm^{-1}.
Anal. Calcd. for $C_{22}H_{23}N_3O_5$: C, 64.71; H, 6.16; N, 8.16; Found: C, 64.59; H, 6.19; N, 8.12.

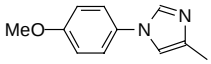


Reaction of (**1** + **6**) clear hard gum, $[\alpha]_D$= 8.0 (c = 0.27 MeOH)

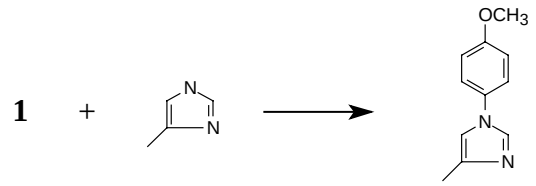
^{1}H NMR (500 MHz, $CDCl_3$) 7.630 (s, 1H), 7.364-7.284 (m, 5H), 7.232 (d, *J* = 9 Hz, 2H), 6.963-6.944 (m, 3H), 6.325 (d, *J* = 8 Hz., 1H), 5.146-5.085 (m, 2H), 4.673-4.657 (m, 1H), 3.831 (s, 3H), 3.721 (s, 3H), 3.191(dq, *J* = 24, 15.5, 5.5, 2H).
^{13}C(125 Hz, $CDCl_3$) 172.3, 159.0, 156.3, 138.2, 136.6, 135.6, 130.6, 128.5, 128.2, 128.1, 123.1, 116.5, 115.0, 66.9, 55.7, 54.0, 52.4, 30.2, 29.4.
IR (neat) 3302, 2975, 1704, 1643, 1493, 1245, 1045 cm^{-1}.
ESIHRMS (M^+ + H) *m / z* 410.1695 ($C_{22}H_{23}N_3O_5$ requires 410.1710).



Reaction of (**5** + 4-methyl imidazole): Clear oil
^{1}H NMR (500 MHz, $CDCl_3$) 7.685 (s, 1H), 7.345 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.265 (dd, *J* = 7, 1.5 Hz, 1H), 7.054-7.007 (m, 2H), 6.917 (s, 1H), 3.852 (s, 3H), 2.303 (s, 3H).
^{13}C(125 Hz, $CDCl_3$) 152.6, 137.9, 137.1, 128.7, 125.5, 121.1, 116.7, 112.4, 55.9, 13.8.
IR (neat) 3377, 2922, 1513, 1290, 1023 cm^{-1}.
ESIHRMS (M^+ + H) *m / z* 189.1032 ($C_{11}H_{12}N_2O$ requires 189.1022).



Reaction of (**1** + 4-methyl imidazole): Solid, mp 78-79 ^{o}C.
^{1}H NMR (500 MHz, $CDCl_3$) 7.645 (s, 1H), 7.275 (d, *J* = 9.5, 2 H), 6.971 (d, *J* = 9, 2 H), 6.920 (s, 1H) 3.841 (s, 3H) 2.289 (s, 3H).
^{13}C(125 Hz, $CDCl_3$) 158.7, 139.3, 134.9, 131.0, 122.9, 115.3, 114.9, 55.7, 13.8.
IR (neat) 3388, 2925, 1519, 1248, 1072 cm^{-1}.
Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88; Found: C, 70.19; H, 6.55; N, 15.04.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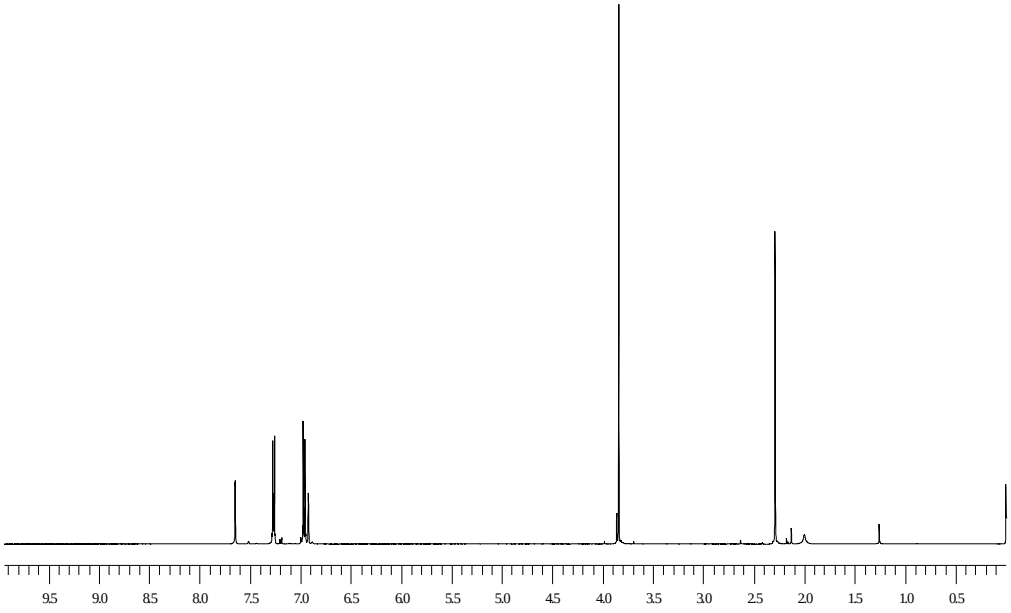
+
OCH3
N
N
N
N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7.0
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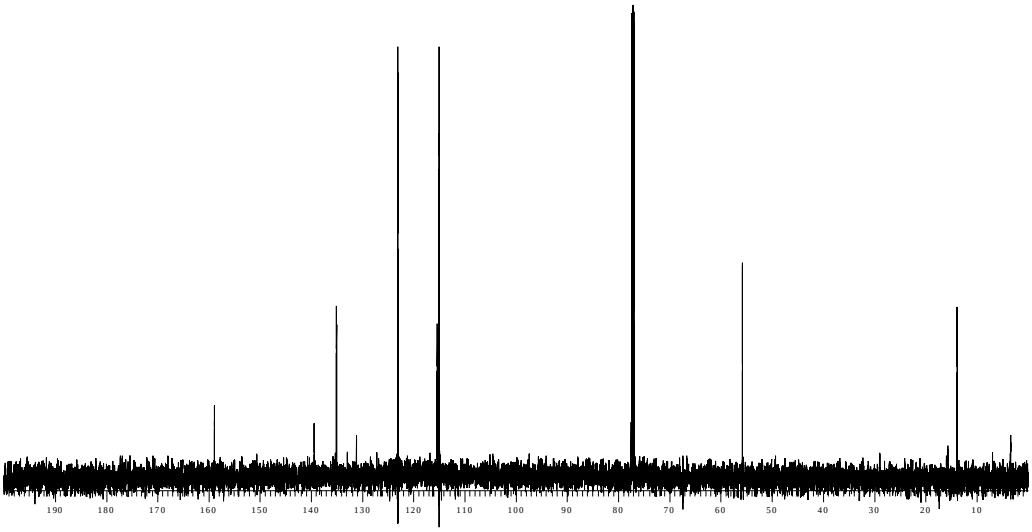
1.5
1.0
0.5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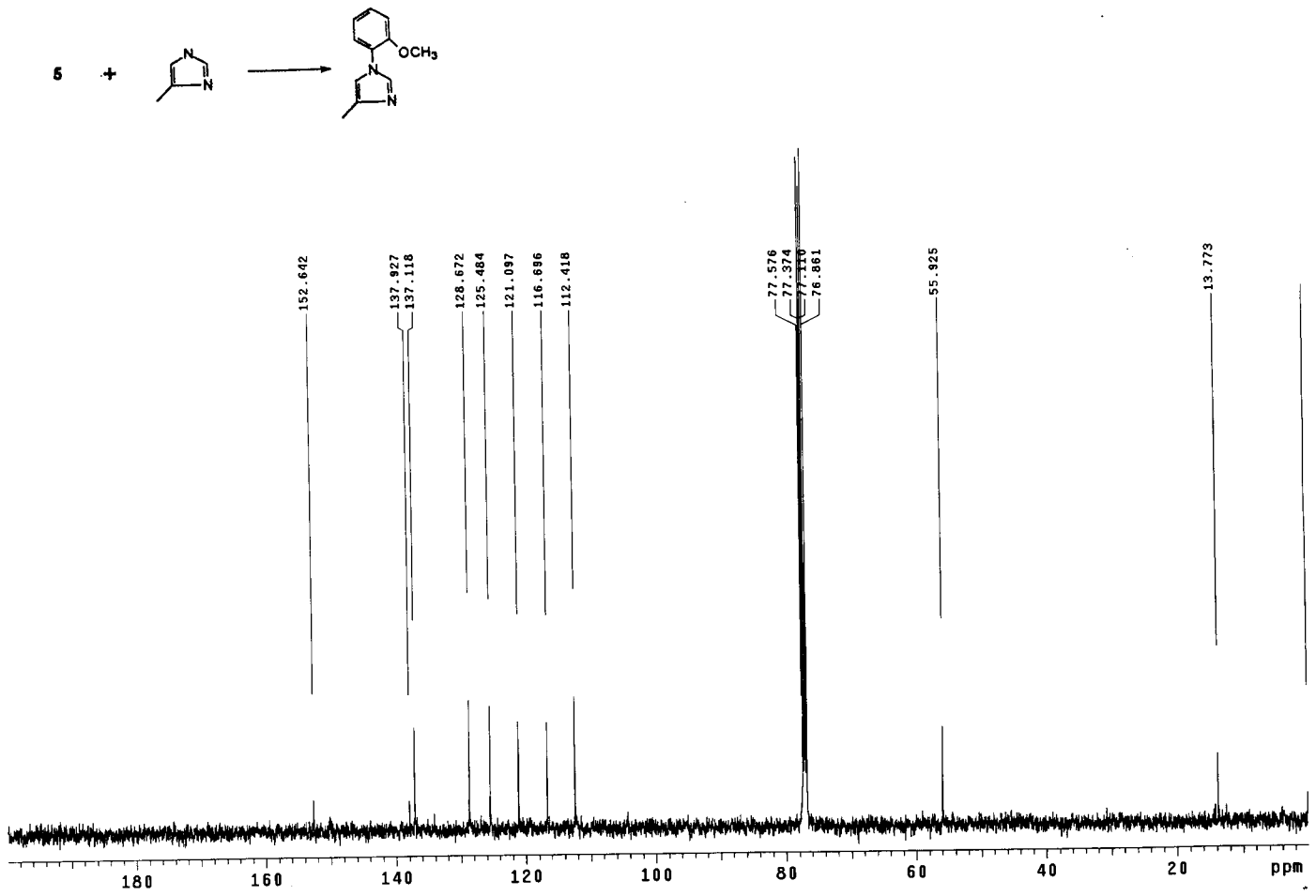
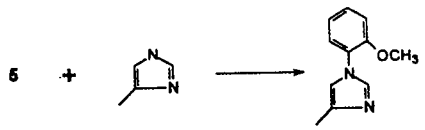
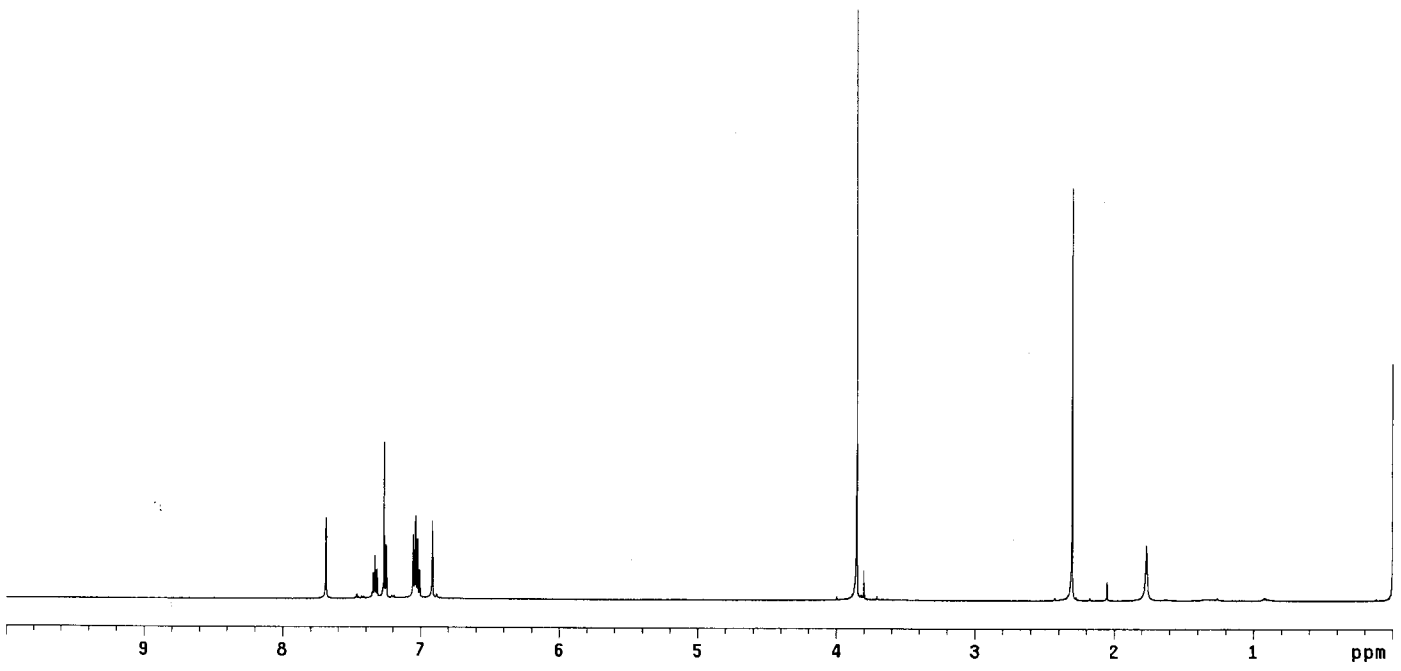


GIE III-218

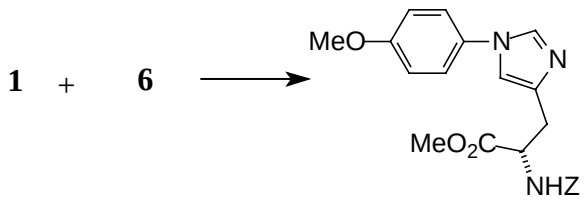
Pulse Sequence: s2pul





GIE III-218

Pulse Sequence: s2pul


1 + 6
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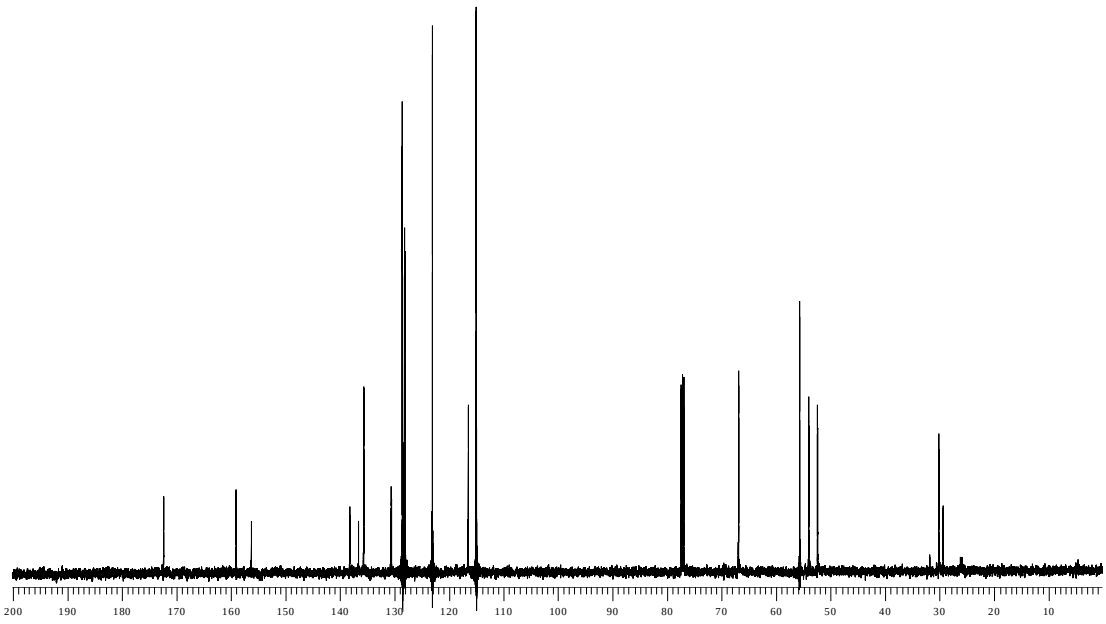
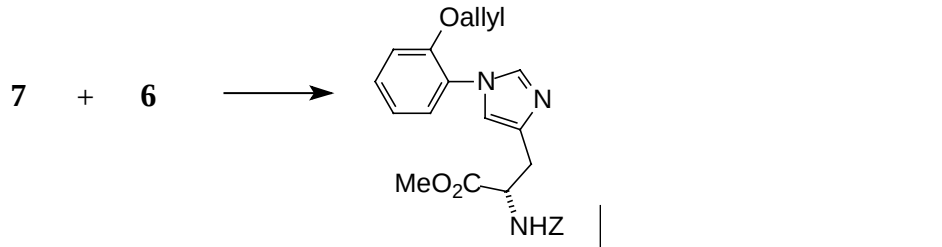
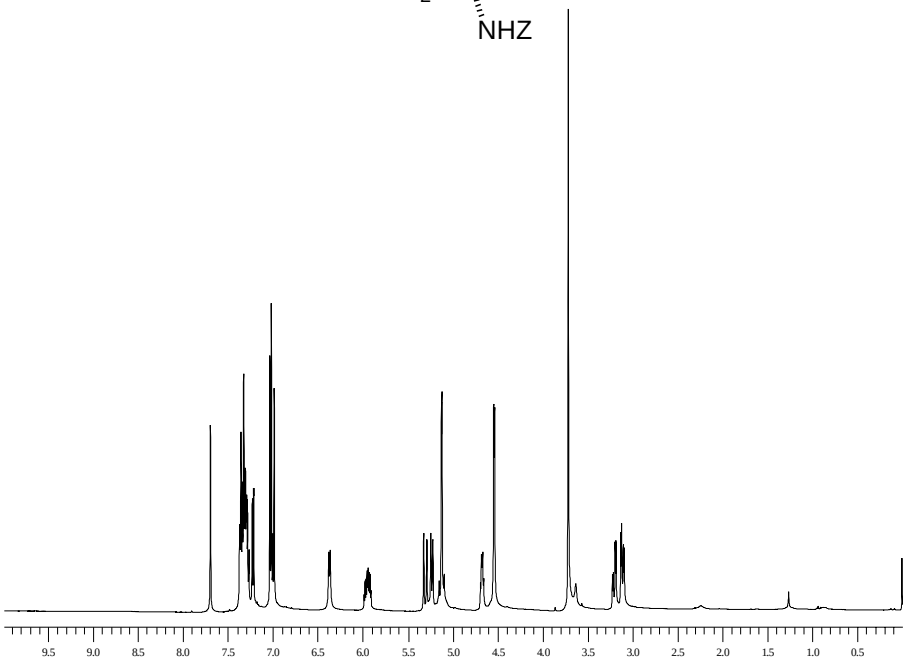
N
N
MeO2C
NHZ




7 + 6
Oallyl
N
N
MeO2C
NHZ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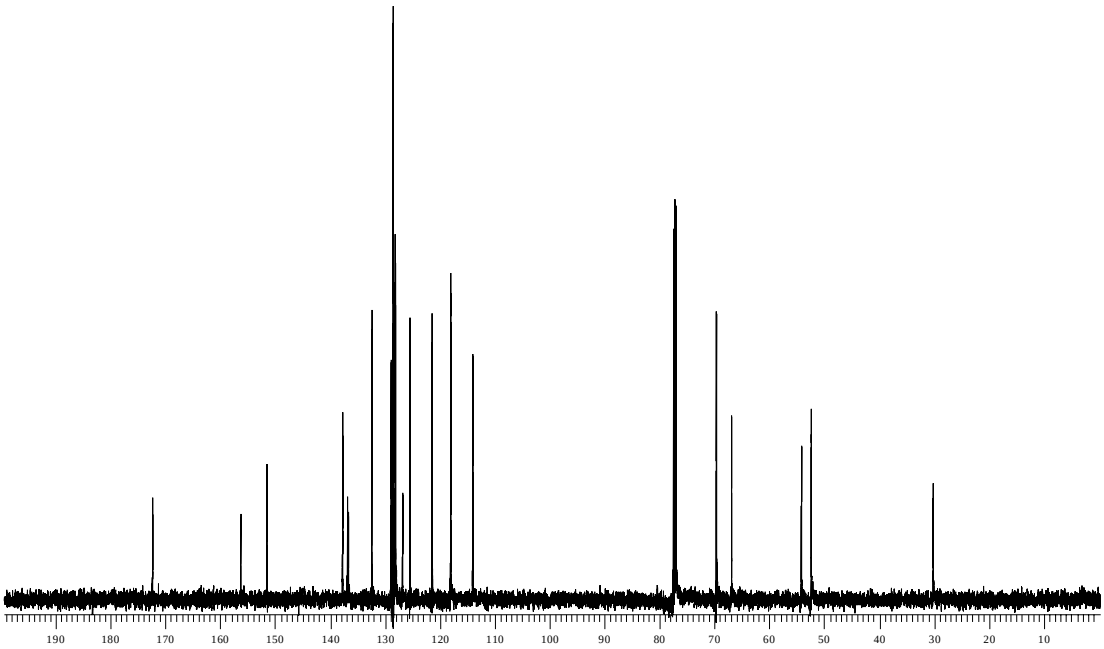
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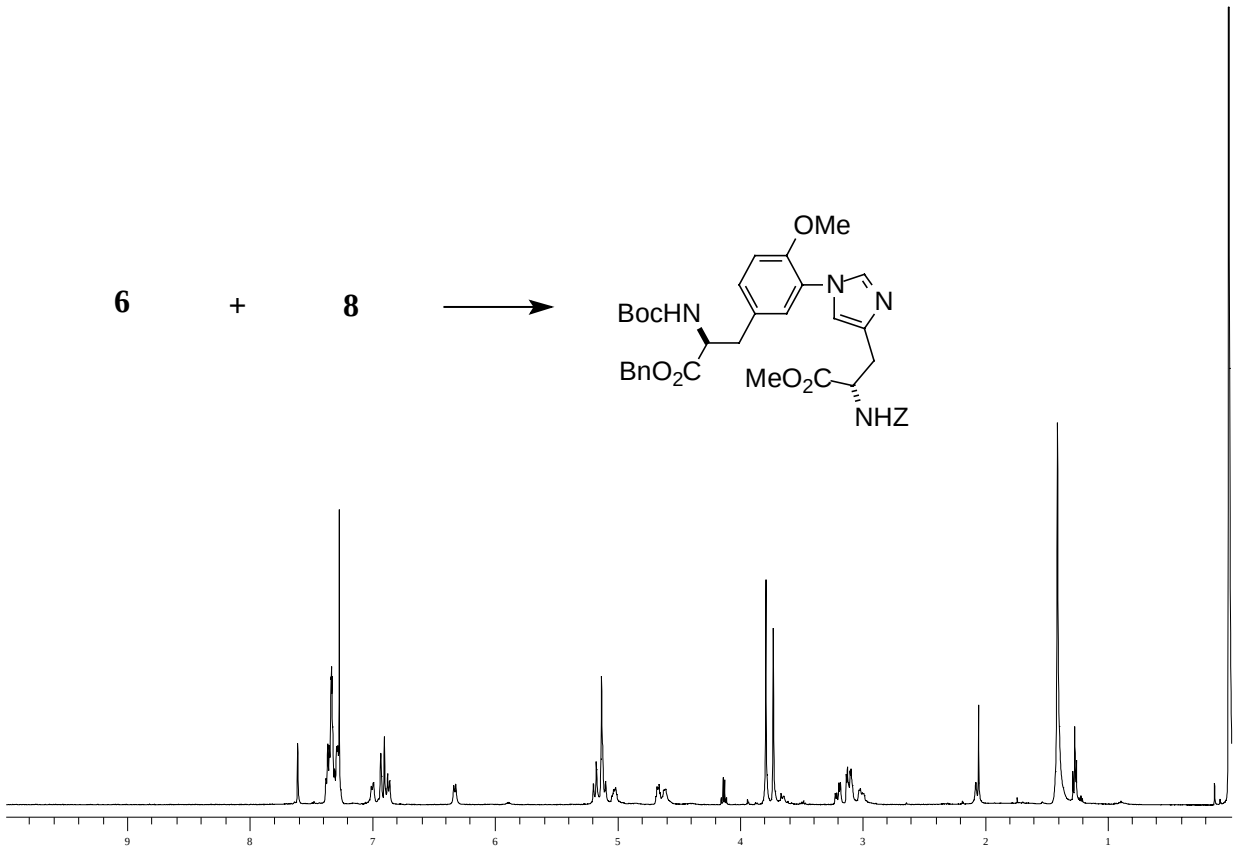
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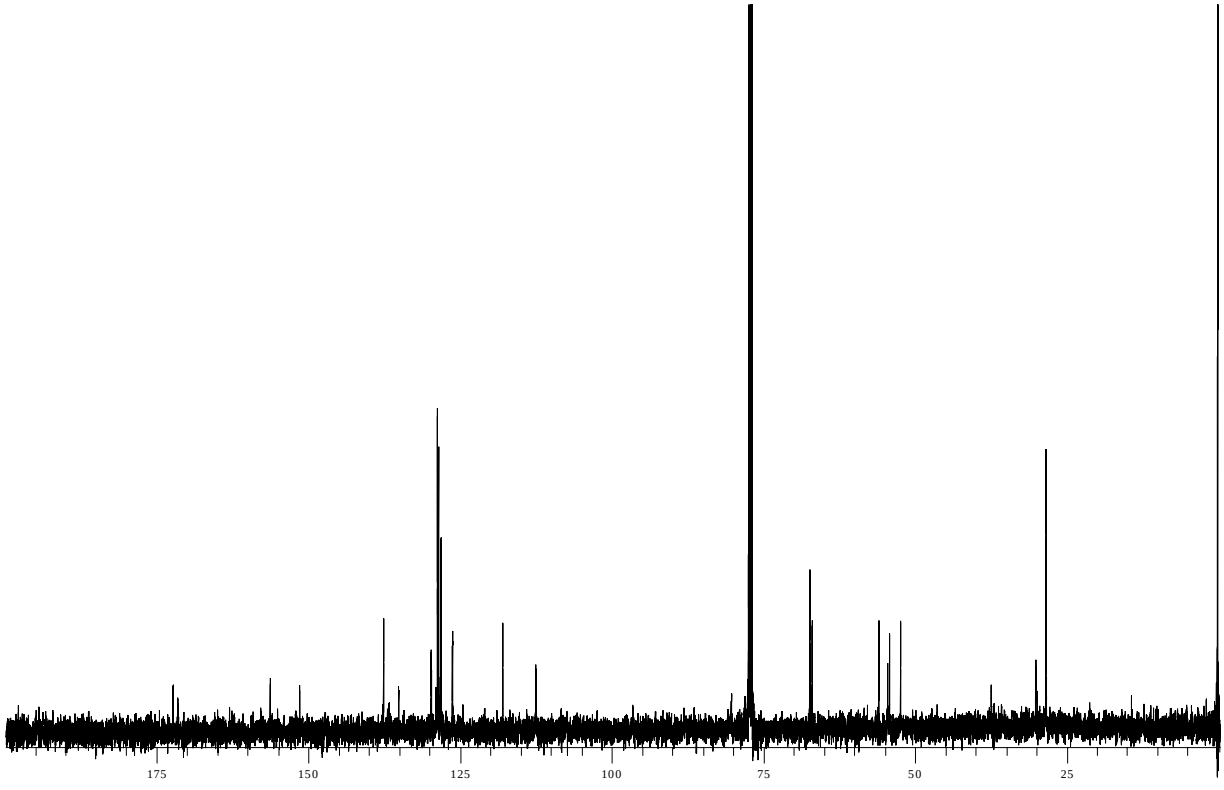
3
2
1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125
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75
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25