

Supporting information

Enantioselective Radical Addition/trapping Reactions with α,β -Disubstituted Unsaturated Imides. Synthesis of *anti*-Propionate Aldols

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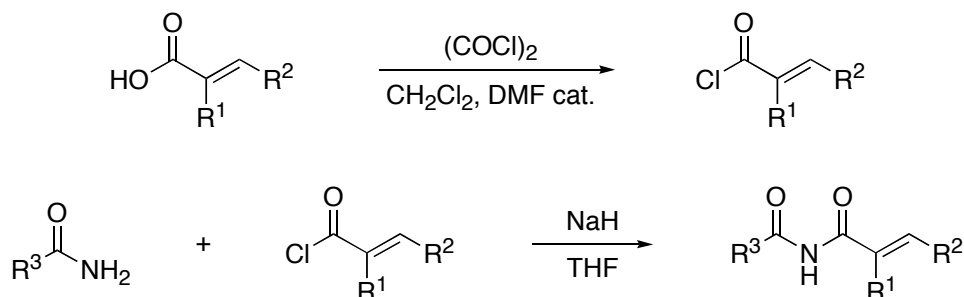
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General: Dichloromethane was distilled from calcium hydride under nitrogen prior to use. Tetrahydrofuran was distilled from sodium benzophenone ketyl under nitrogen. Magnesium perchlorate, Magnesium iodide and Magnesium triflimide were purchased from Aldrich chemicals. Cyclopropyl bisoxazoline ligand {3aS-[2(3'aR, 8'aS), 3aa, 8aa]}-2,2'-(cyclopropylidene)-bis{3a,8a-dihydro-8H-indeno[1,2d]-oxazole} was prepared according to literature procedure. Flash chromatography was performed using EM Science silica gel 60 (230-400 mesh). All glassware was oven dried, assembled hot and cooled under a stream of nitrogen before use. Reactions with air sensitive materials were carried out by standard syringe techniques.

Melting points were measured with a Fisher-Johns melting points apparatus and are uncorrected ^1H -NMR were recorded on a Varian Unity/Inova-500 NB (500 MHz) or Varian Unity/Inova-400 NB (400 MHz). Chemical shifts are reported in parts per million (ppm) down field from TMS, using residual CDCl_3 (7.27 ppm) as an internal standard. Data are reported as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant and integration. ^{13}C -NMR was recorded in a Varian Unity/Inova-500 NB (125 MHz) or Varian Unity/Inova-400 NB (100 MHz) spectrometers, using broadband proton decoupling. Chemical shifts are reported in parts per million (ppm) downfield from TMS, using the middle resonance of CDCl_3 (77.0) as an internal standard. HPLC analyses were carried out on Waters 515 HPLC pump and a 2487 dual λ absorbance detector connected to a PC with Millennium workstation. GC analyses were performed on a Hewlett Packard 5890 Series II gas chromatograph using helium as carrier gas. Rotation were recorded on a JASCO-DIP-370

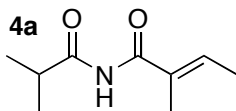
instrument. High Resolution Mass Spectra (HRMS) (EI+) were obtained from Mass Spectrometry Laboratory, Ohio State University, Columbus, Ohio.

General procedure for the synthesis of α,β -unsaturated imides:

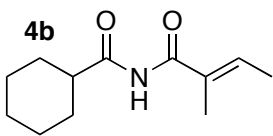


To a cold solution of α,β -unsaturated acid (11.0 mmol) in 15 mL of dichloromethane at 0 °C, under nitrogen, oxalyl chloride (12.1 mmol) was added drop wise followed by addition of a drop of DMF. The mixture was stirred at 0 °C for 10 min, and at room temperature for two hours. The solvent and excess of oxalyl chloride were removed *in vacuo* to give crude chloride which was further used without purification.

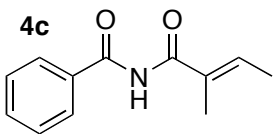
In a separate flask, 11.0 mmol of carboxamide was dissolved in 46 mL of dry THF, and obtained solution was cooled at 0 °C, under nitrogen. This was followed by portion wise addition of sodium hydride (22.0 mmol, 60% dispersion in mineral oil). The mixture was stirred at 0 °C for 10 min, and at room temperature for 45 min. The reaction was cooled at 0 °C, and a solution of prepared chloride (11.0 mmol) in 10 mL of dry THF was added drop wise. The reaction mixture was stirred at 0 °C for 10 min and at room temperature for 4 hours. After completion of reaction, it was quenched by the addition of 10 ml of 1.5 M hydrochloric acid, and diluted with ethyl acetate (200 mL). The organic phase was separated, washed successively with saturated aqueous sodium bicarbonate, brine and dried with anhydrous magnesium sulfate. The solvent was removed *in vacuo*, and the residue was purified by silica gel chromatography.



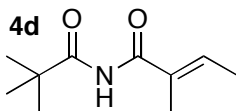
N-(*E*-2-Methylbut-2-enoyl)-dimethylacetamide (4a). This imide was obtained according to the general procedure in 61% yield as a white solid m.p. = 108-109 °C. ¹H-NMR (500 MHz, CDCl₃) δ 1.19 (d, J = 6.5 Hz, 6H), 1.83 (dq, J = 7.0, 1.0 Hz, 3H), 1.87 (quin, J = 1.0 Hz, 3H), 3.52 (hep, J = 6.5 Hz, 1H), 6.54 (qq, J = 7.0, 1.0 Hz, 1H), 8.02 (s, broad, 1H); ¹³C-NMR (125 MHz, CDCl₃) δ 180.2, 167.1, 134.7, 132.3, 34.9, 18.9, 14.6, 12.4. HRMS calcd. for C₉H₁₅NO₂Na⁺ 192.0995 found 192.0992.



N-(*E*-2-Methylbut-2-enoyl)-cyclohexanecarboxamide (4b). This imide was furnished according to the general procedure in 63% yield as a white solid. m.p. = 115-116 °C. ¹H-NMR (500 MHz, CDCl₃) δ 1.23 (qt, J = 12.5, 3.5 Hz, 1H), 1.35 (qt, J = 12.5, 3.5 Hz, 2H), 1.43 (qd, J = 12.5, 3.0 Hz, 2H), 1.66-1.72 (m, 1H), 1.79 (dt, J = 12.5, 3.5 Hz, 2H), 1.82 (dq, J = 7.0, 1.0 Hz, 3H), 1.87 (quin, J = 1.0 Hz, 3H), 1.89-1.95 (m, 2H), 3.25 (tt, J = 11.5, 3.5 Hz, 1H), 6.53 (qq, J = 7.0, 1.0 Hz, 1H), 7.98 (s, broad, 1H); ¹³C-NMR (125 MHz, CDCl₃) δ 178.9, 167.0, 134.6, 132.4, 44.5, 29.1, 26.0, 25.8, 14.6, 12.4. HRMS calcd. for C₁₂H₁₉NO₂Na⁺ 232.1308 found 232.1300.

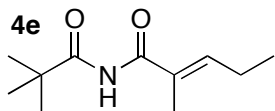


N-(*E*-2-Methylbut-2-enoyl)-benzamide (4c). This compound was obtained according to the general procedure for the imide synthesis in 43% yield as a white solid m.p. = 108-109 °C. ¹H-NMR (500 MHz, CDCl₃) δ 1.85 (dq, J = 7.0, 1.0 Hz, 3H), 1.93 (quin, J = 1.0 Hz, 3H), 6.57 (qq, J = 7.0, 1.0 Hz, 1H), 7.48 (t, J = 8.0 Hz, 2H), 7.58 (tt, J = 7.5, 1.0 Hz, 1H), 7.79 (dd, J = 8.0, 1.0 Hz, 2H), 8.51 (s, broad, 1H); ¹³C-NMR (125 MHz, CDCl₃) δ 168.3, 166.7, 134.9, 133.8, 133.0, 132.9, 128.9, 128.0, 14.6, 12.6. HRMS calcd. for C₁₂H₁₃NO₂Na⁺ 226.0838 found 226.0827.

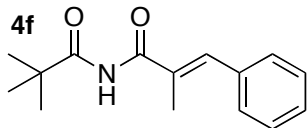


N-(*E*-2-Methylbut-2-enoyl)-trimethylacetamide (4d). The imide was obtained according to the general procedure in 86% yield as a white solid m.p. = 102-103 °C. ¹H-NMR (500 MHz, CDCl₃) δ 1.26 (s, 9H), 1.82 (dq, J = 7.0, 1.0 Hz, 3H), 1.87 (quin, J = 1.0 Hz, 3H), 6.39 (qq, J = 7.0, 1.0

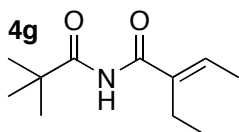
Hz, 1H), 8.15 (s, broad, 1H); ^{13}C -NMR (125 MHz, CDCl_3) δ 176.1, 168.2, 133.8, 133.3, 40.6, 27.3, 14.4, 12.6. HRMS calcd. for $\text{C}_{10}\text{H}_{17}\text{NO}_2\text{Na}^+$ 206.1151 found 206.1169.



N-(*E*-2-Methylpent-2-enoyl)-trimethylacetamide (4e). This imide was prepared according to the general procedure in 81% yield as a white solid m.p. = 101-102 °C. ^1H -NMR (400 MHz, CDCl_3) δ 1.01 (t, J = 7.6 Hz, 3H), 1.22 (s, 9H), 1.82 (s, 3H), 2.16 (quin, J = 7.6 Hz, 2H), 6.22 (td, J = 7.2, 1.2 Hz, 1H), 8.19 (s, broad, 1H); ^{13}C -NMR (100 MHz, CDCl_3) δ 176.1, 168.3, 140.6, 131.7, 40.5, 27.3, 22.0, 13.1, 12.7. HRMS calcd. for $\text{C}_{11}\text{H}_{19}\text{NO}_2\text{Na}^+$ 220.1308 found 220.1309.

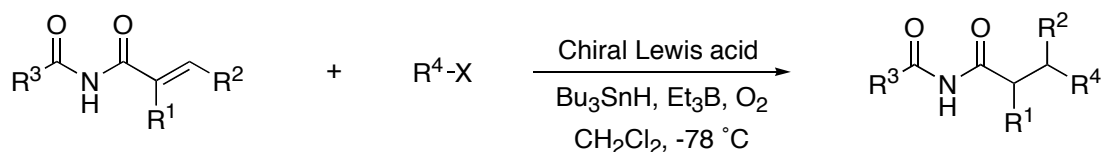


N-(*E*-2-Methyl-3-phenylprop-2-enoyl)-trimethylacetamide (4f). This imide was furnished according to the general procedure in 81% yield as a white solid m.p. = 93-94 °C. ^1H -NMR (500 MHz, CDCl_3) δ 1.30 (s, 9H), 2.15 (d, J = 1.5 Hz, 3H), 7.22 (s, broad, 1H); 7.31-7.36 (m, 1H), 7.37-7.43 (m, 4H), 8.25 (s, broad, 1H); ^{13}C -NMR (125 MHz, CDCl_3) δ 176.2, 169.4, 136.6, 136.1, 135.5, 132.9, 129.8, 129.7, 128.7, 128.7, 40.6, 27.3, 14.7. HRMS calcd. for $\text{C}_{15}\text{H}_{19}\text{NO}_2\text{Na}^+$ 268.1308 found 268.1314.



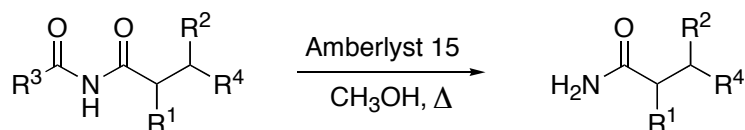
N-(*E*-2-Ethylbut-2-enoyl)-trimethylacetamide (4g). The imide was prepared according to the general procedure in 40% yield as a white solid m.p. = 110-111 °C. ^1H -NMR (500 MHz, CDCl_3) δ 1.04 (t, J = 7.5 Hz, 3H), 1.26 (s, 9H), 1.83 (d, J = 7.0 Hz, 3H), 2.36 (q, J = 7.5 Hz, 2H), 6.29 (q, J = 7.0 Hz, 1H), 8.15 (s, broad, 1H); ^{13}C -NMR (125 MHz, CDCl_3) δ 176.0, 167.8, 139.8, 132.6, 40.6, 27.3, 20.3, 14.1, 13.3. HRMS calcd. for $\text{C}_{11}\text{H}_{19}\text{NO}_2\text{Na}^+$ 220.1308 found 220.1302.

General procedure for enantioselective reductive alkyl radical additions to α,β -disubstituted imides:

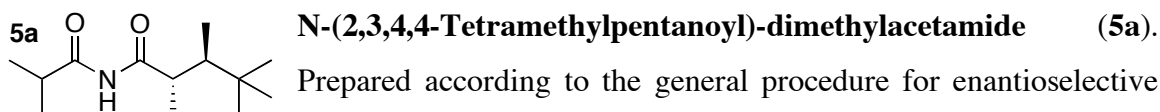


Chiral ligand (0.062 mmol) and corresponding Lewis acid (0.06 mmol) in 1.0 mL of dichloromethane were stirred vigorously at room temperature for 45 min, and cooled at $-78\text{ }^\circ\text{C}$. The α,β -unsaturated imide (0.2 mmol) was added to the cold reaction mixture as a solution in 1.0 mL of dichloromethane, and obtained mixture was stirred at $-78\text{ }^\circ\text{C}$ for 30 min before initiation. The reaction was initiated by sequential addition of alkyl halide (1.0 mmol), tributyltin hydride (0.4 mmol), triethylborane (0.6 mmol) and oxygen. The reaction was monitored by TLC, and after completion was quenched by silica gel, evaporated, washed with hexanes, toluene and extracted with 20% ethyl acetate in hexanes. The crude product was purified by silica gel chromatography. Racemic standards were prepared using $\text{Yb}(\text{OTf})_3$ as a Lewis acid in the absence of a chiral ligand and methylene chloride:tetrahydrofuran (2:1) as a solvent.

General procedure for selective methanolysis of imides:¹



To a solution of product-imide (0.55 mmol) in 10.0 mL of dry methanol Amberlyst 15 (2.90 g) was added, and obtained mixture was heated at $80\text{ }^\circ\text{C}$. The reaction was monitored by TLC, and after completion was cooled at room temperature. The cold mixture was filtered and Amberlyst 15 was washed with dichloromethane (5 x 15 mL). The combined organics were evaporated to give crude amide. The crude product was purified by silica gel chromatography.



alkyl radical addition reaction using $\text{Mg}(\text{NTf}_2)_2$ as Lewis acid, cyclopropyl (1*S*, 2*R*)-inda-box **7** and *tert*-butyl iodide. The product was obtained as a white crystalline solid in 69% yield, as a mixture of two diastereomers in ratio 97:3 according to ^1H -NMR. $[\alpha] = +23.4^\circ$ (*c* 0.5, CH_2Cl_2) ^1H -NMR (400 MHz, CDCl_3) δ 0.89 (s, 9H), 1.03 (d, *J* = 7.6 Hz, 3H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.21 (d, *J* = 7.2 Hz, 3H), 1.40 (qd, *J* = 7.2 Hz, *J* = 3.6 Hz, 1H), 2.93-3.04 (m, 1H), 3.17 (quin, *J* = 6.8 Hz, 1H), 8.19 (s, broad, 1H); ^{13}C -NMR (100 MHz, CDCl_3) δ 179.1, 176.9, 48.5, 41.7, 35.4, 34.2, 28.4, 19.2, 18.9, 18.7, 11.3. HRMS calcd. for $\text{C}_{13}\text{H}_{25}\text{NO}_2\text{Na}^+$ 250.1777 found 250.1782.

Assay of enantiomeric excess. Product enantiomeric excess was determined by two step conversion to N-(2,3,4,4-tetramethylpentanoyl)-benzamide **5c**. The imide **5a** was

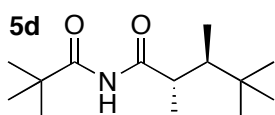
selectively methanolized, according to the general procedure, to give 2,3,4,4-tetramethylpentamide **5a'** in 83% yield, as a white crystalline solid. ^1H -NMR (400 MHz, CDCl_3) δ 0.91 (s, 9H), 0.99 (d, *J* = 7.6 Hz, 3H), 1.18 (d, *J* = 6.8 Hz, 3H), 1.33 (qd, *J* = 7.2, 3.6 Hz, 1H), 2.49 (qd, *J* = 6.8, 3.6 Hz, 1H), 5.30-5.70 (m, 2H); ^{13}C -NMR (100 MHz, CDCl_3) δ 179.1, 47.8, 41.3, 34.2, 28.3, 19.7, 11.2. HRMS calcd. for $\text{C}_9\text{H}_{19}\text{NONa}^+$ 180.1358 found 180.1359.

Amide **5a'** was converted to N-(2,3,4,4-tetramethylpentanoyl)-benzamide **5c**, according to the general procedure for imide synthesis in 45% yield, whose ^1H and ^{13}C spectra are same as for imide **5c**. Enantiomeric excess (69%) was determined by chiral HPLC analysis under same conditions as for imide **5c** (chiralcel AD column (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.), solvent Hexanes: Isopropanol = 99 : 1, flow rate 0.5 mL/min; $t_{\text{r}}(\text{major}) = 24.0$ min, $t_{\text{r}}(\text{minor}) = 34.5$ min).

N-(2,3,4,4-Tetramethylpentanoyl)-cyclohexanecarboxamide (5b). Prepared according to the general procedure for enantioselective alkyl radical addition reaction using

$\text{Mg}(\text{NTf}_2)_2$ as Lewis acid, cyclopropyl (1*S*, 2*R*)-inda-box **7** and *tert*-butyl iodide. The product was obtained as a white crystalline solid in 67% yield, as a mixture of two diastereomers in ratio 98:2 according to ^1H -NMR. m.p. = 139-140 °C. $[\alpha] = +15.8^\circ$ (*c* 1.0, CHCl_3). ^1H -NMR(400 MHz, CDCl_3) δ 0.89 (s, 9H), 1.03 (d, *J* = 7.6 Hz, 3H), 1.21 (d, *J* = 6.8 Hz,

3H), 1.14-1.46 (m, 6H), 1.63-1.71 (m, 1H), 1.73-1.81 (m, 2H), 1.82-1.92 (m, 2H), 2.81-2.91 (m, 1H), 2.92-3.02 (m, 1H), 7.75 (s, broad, 1H); ^{13}C -NMR (100 MHz, CDCl_3) δ 177.7, 176.8, 48.5, 45.1, 41.8, 34.2, 29.1, 28.9, 28.4, 25.9, 25.7, 25.6, 19.2, 11.4. HRMS calcd. for $\text{C}_{16}\text{H}_{29}\text{NO}_2\text{Na}^+$ 290.2090 found 290.2091. Enantiomeric excess (65%) was determined by chiral HPLC analysis (chiralcel AD column (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.), solvent Hexanes: Isopropanol = 99:1, flow rate 0.5 mL/min; $t_{\text{r (major)}} = 17.8$ min, $t_{\text{r (minor)}} = 27.1$ min).



N-(2,3,4,4-Tetramethylpentanoyl)-trimethylacetamide (5d).

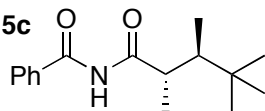
Obtained according to the general procedure for enantioselective alkyl radical addition reaction using MgI_2 as a Lewis acid, cyclopropyl (1*S*, 2*R*)-inda-box **7** and *tert*-butyl iodide. The adduct was obtained as a white crystalline solid in 83% yield, as a mixture of two diastereomers in the ratio 99:1 according to ^1H -NMR. m.p. = 111-112 °C. $[\alpha]_{\text{D}} = +40.5^\circ$ (c 1.0, CHCl_3) ^1H -NMR(400 MHz, CDCl_3) δ 0.87 (s, 9H), 1.05 (d, $J = 6.8$ Hz, 3H), 1.20 (d, $J = 7.2$ Hz, 3H), 1.22 (s, 9H), 1.43 (qd, $J = 7.2, 3.6$ Hz, 1H), 3.77 (qd, $J = 6.8, 3.6$ Hz, 1H), 7.89 (s, broad, 1H); ^{13}C -NMR (100 MHz, CDCl_3) δ 179.5, 176.8, 48.7, 40.4, 39.4, 34.2, 28.5, 27.2, 18.9, 11.6. HRMS calcd. for $\text{C}_{14}\text{H}_{27}\text{NO}_2\text{Na}^+$ 264.1933 found 264.1939.

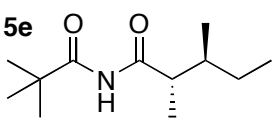
Assay of enantiomeric excess. Product enantiomeric excess was determined by two step conversion to N-(2,3,4,4-tetramethylpentanoyl)-benzamide **5c**. The imide **5d** was selectively methanolized, according to the general procedure, to give 2,3,4,4-tetramethylpentamide **5a'** in 78% yield, as a white crystalline solid.

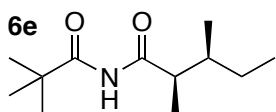
Amide **5a'** was converted to N-(2,3,4,4-tetramethylpentanoyl)-benzamide **5c**, according to the general procedure for imide synthesis in 41% yield, which ^1H and ^{13}C spectra are same as for imide **5c**. m. p. = 136-137 °C. $[\alpha]_{\text{D}} = +12.8^\circ$ (c 1.0, CHCl_3). Enantiomeric excess (94%) was determined by chiral HPLC analysis under same conditions as for imide **5c** (chiralcel AD column (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.), solvent Hexanes:Isopropanol = 99:1, flow rate 0.5 mL/min; $t_{\text{r (major)}} = 24.0$ min, $t_{\text{r (minor)}} = 34.5$ min).

The same value for enantiomeric excess was obtained by direct analysis of N-(2,3,4,4-tetramethylpentanoyl)-trimethylacetamide **5c**, by chiral GC analysis (BETA DEXTM 120

Capillary Column; oven temp = 90 °C, flow rate = 15.7 mL/min, $t_{r(\text{major})}$ = 35.2 min, $t_{r(\text{minor})}$ = 31.9 min).

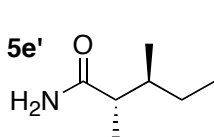
5c  **N-(2,3,4,4-Tetramethylpentanoyl)-benzamide (5c).** Prepared according to the general procedure for enantioselective alkyl radical addition reaction using $\text{Mg}(\text{ClO}_4)_2$ as Lewis acid, cyclopropyl (1*S*, 2*R*)-inda-box **7** as a chiral ligand and *tert*-butyl iodide. The product was obtained as a white crystalline solid in 78% yield, as a separable mixture of two diastereomers in ratio 98:2 according to ^1H -NMR. $[\alpha] = +14.8^\circ$ (c 0.5, CH_2Cl_2) ^1H -NMR (300 MHz, CDCl_3) δ 0.93 (s, 9H), 1.12 (d, $J = 7.5$ Hz, 3H), 1.31 (d, $J = 7.5$ Hz, 3H), 1.51 (qd, $J = 7.2, 3.6$ Hz, 1H), 3.92 (qd, $J = 6.9, 3.6$ Hz, 1H), 7.49 (t, $J = 7.8$ Hz, 2H), 7.60 (t, $J = 7.8$ Hz, 1H), 7.87 (d, $J = 7.8$ Hz, 2H), 8.68 (s, broad, 1H); ^{13}C -NMR (75 MHz, CDCl_3) δ 179.7, 165.7, 133.4, 133.3, 129.1, 127.9, 48.8, 39.7, 34.4, 28.6, 19.1, 11.6. HRMS calcd. for $\text{C}_{16}\text{H}_{23}\text{NO}_2\text{Na}^+$ 284.1620 found 284.1619. Enantiomeric excess (79%) was determined by chiral HPLC analysis (chiralcel AD column (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.), solvent Hexanes: Isopropanol = 99:1, flow rate 0.5 mL/min; $t_{r(\text{major})}$ = 24.0 min, $t_{r(\text{minor})}$ = 34.5 min).

5e  **N-(2,3-Dimethylpentanoyl)-trimethylacetamide (5e and 6e).** Prepared according to the general procedure for enantioselective alkyl radical addition reaction using MgI_2 as Lewis acid, cyclopropyl (1*S*, 2*R*)-inda-box **7** as a chiral ligand and ethyl iodide. The product was obtained as a white crystalline solid in 63% yield, as an inseparable mixture of two diastereomers in ratio 87:13 according to ^1H -NMR. The *anti* diastereomer can be obtained as a pure compound by careful chromatography. Major *anti* **5e**: m.p. = 87-88 °C. $[\alpha]_D = +18.3^\circ$ (c 1.0, CHCl_3). ^1H -NMR (400 MHz, CDCl_3) δ 0.84 (t, $J = 7.6$ Hz, 3H), 0.92 (d, $J = 6.8$ Hz, 3H), 1.07 (d, $J = 6.8$ Hz, 3H), 1.05-1.15 (m, 1H), 1.22 (s, 9H), 1.45 (dq, $J = 13.6, 7.6, 3.6$ Hz, 1H), 1.69 (dq, $J = 9.6, 6.8, 3.6$ Hz, 1H), 3.37 (quin, $J = 6.8$ Hz, 1H), 7.95 (s, broad, 1H); ^{13}C -NMR (100 MHz, CDCl_3) δ 179.4, 176.9, 44.9, 40.4, 37.1, 27.2, 24.9, 17.4, 13.3, 11.5. HRMS calcd. for $\text{C}_{12}\text{H}_{23}\text{NO}_2\text{Na}^+$ 236.1620 found 236.1631.



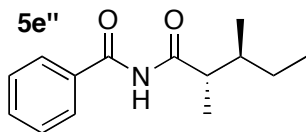
Minor *syn* **6e**: $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 0.84 (d, $J = 6.5$ Hz, 3H), 0.90 (t, $J = 7.2$ Hz, 3H), 1.05 (d, $J = 7.0$ Hz, 3H), 1.24 (s, 9H), 1.16-1.27 (m, 1H); 1.32-1.42 (m, 1H); 1.72-1.81 (m, 1H); 3.46 (quin, $J = 6.5$ Hz, 1H), 7.98 (s, broad, 1H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 179.6, 176.8, 44.1, 40.4, 36.4, 28.1, 27.2, 17.4, 14.7, 11.8. HRMS calcd. for $\text{C}_{12}\text{H}_{23}\text{NO}_2\text{Na}^+$ 236.1620 found 236.1631.

Assay of enantiomeric excess. Enantiomeric excess of major diastereomer **5e** (92%) was determined by two step conversion to N-(2,3-dimethylpentanoyl)-benzamide. The product was methanolized according to the general procedure. The amide 2,3-



dimethylpentanoylamide **5e'**, was obtained as a white crystalline solid in 61% yield as a mixture of two diastereomers in the same ratio 87:13. Major *anti* amide **5e'**: m.p. = 111-112 °C. $[\alpha]_D = + 12.6^\circ$ (c 1.0, CHCl_3). $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 0.88 (t, $J = 7.5$ Hz, 3H), 0.93 (d, $J = 6.5$ Hz, 3H), 1.13 (d, $J = 7.0$ Hz, 3H), 1.11-1.20 (m, 1H), 1.53 (dq, $J = 13.5, 7.5, 4.0$ Hz, 1H), 1.58-1.65 (m, 1H), 2.10 (quin, $J = 7.0$ Hz, 1H), 5.30-5.70 (m, 2H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 178.9, 46.2, 37.7, 25.9, 17.0, 15.1, 11.2. HRMS calcd. for $\text{C}_7\text{H}_{15}\text{NONa}^+$ 152.1045 found 152.1042.

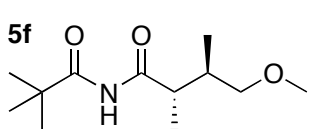
Amide **5e'** was converted to N-(2,3-dimethylpentanoyl)-benzamide **5e''**, according to the general procedure for imide synthesis. The imide **5** was



obtained as a white crystalline solid in 37% yield as a mixture of two diastereomers in the same ratio 87:13. $[\alpha] = + 8.4^\circ$ (c 0.5, CH_2Cl_2). Major *anti* benzimide **5e''**: $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 0.90 (t, $J = 7.5$ Hz, 3H), 1.10 (d, $J = 7.0$ Hz, 3H), 1.15-1.21 (m, 1H), 1.19 (d, $J = 6.5$ Hz, 3H), 1.54 (dq, $J = 13.5, 7.5, 3.5$ Hz, 1H), 1.84 (dq, $J = 9.5, 6.5, 3.5$ Hz, 1H), 3.49 (quin, $J = 7.0$ Hz, 1H), 7.50 (t, $J = 8.0$ Hz, 2H), 7.60 (t, $J = 7.5$ Hz, 1H), 7.84 (d, $J = 8.5$ Hz 2H), 8.41 (s, broad, 1H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 179.1, 165.4, 133.4, 133.3, 129.2, 127.8, 45.3, 37.2, 25.0, 17.4, 13.4, 11.5. HRMS calcd. for $\text{C}_{14}\text{H}_{19}\text{NO}_2\text{Na}^+$ 256.1308 found 256.1309.

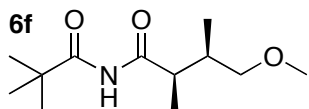
Enantiomeric excess (92%) was determined by chiral HPLC analysis (two connected chiralcel AS columns (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.), solvent

Hexanes: Isopropanol = 99:1, flow rate 0.5 mL/min; $t_{r(\text{major})}$ = 71.6 min, $t_{r(\text{minor})}$ = 83.6 min. Retention times for *syn* enantiomers are 65.0 min and 78.6 min.)



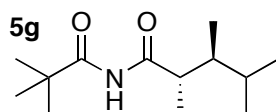
N-(2,3-Dimethyl-4-methoxybutanoyl)-trimethylacetamide (5f and 6f). Prepared according to the general procedure for enantioselective alkyl radical addition reaction using MgI_2 as

Lewis acid, cyclopropyl (1*S*, 2*R*)-inda-box **7** as a chiral ligand and bromomethyl methyl ether. The product was obtained as a white crystalline solid in 59% yield, as an inseparable mixture of two diastereomers in ratio 3:1 according to ^1H -NMR. Major *anti* **5f**: ^1H -NMR (500 MHz, CDCl_3) δ 0.96 (d, J = 7.0 Hz, 3H), 1.14 (d, J = 7.0 Hz, 3H), 1.23 (s, 9H), 2.09 (dhex, J = 7.0, 5.5 Hz, 1H), 3.19 (dq, J = 7.0, 5.5 Hz, 1H), 3.24-3.39 (m, 2H), 3.34 (s, 3H), 8.38 (s, broad, 1H); ^{13}C -NMR (125 MHz, CDCl_3) δ 176.8, 176.6, 75.4, 59.0, 42.8, 40.4, 36.0, 27.1, 14.9, 13.8. HRMS calcd. for $\text{C}_{12}\text{H}_{23}\text{NO}_3\text{Na}^+$ 252.1570 found 252.1563.



Minor *syn* **6f**: ^1H -NMR(500 MHz, CDCl_3) δ 0.91 (d, J = 7.0 Hz, 3H), 1.10 (d, J = 7.0 Hz, 3H), 1.24 (s, 9H), 2.16 (hep, J = 7.0 Hz, 1H), 3.24-3.39 (m, 3H), 3.30 (s, 3H), 8.01 (s, broad, 1H);

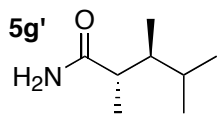
^{13}C -NMR (125 MHz, CDCl_3) δ 178.7, 176.7, 76.8, 59.0, 42.2, 40.4, 35.4, 27.2, 13.5, 13.2. HRMS calcd. for $\text{C}_{12}\text{H}_{23}\text{NO}_3\text{Na}^+$ 252.1570 found 252.1563. Enantiomeric excess (56%) was determined by chiral HPLC analysis (two connected chiralcel AD columns (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.), solvent Hexanes:Isopropanol = 99:1, flow rate 0.5 mL/min; $t_{r(\text{major})}$ = 53.3 min, $t_{r(\text{minor})}$ = 42.5 min. Retention times for *syn* enantiomers are 42.5 min and 47.1 min.).



N-(2,3,4-Trimethylpentanoyl)-trimethylacetamide (5g).

Obtained according to the general procedure for enantioselective alkyl radical addition reaction using MgI_2 as Lewis acid, cyclopropyl (1*S*, 2*R*)-inda-box **7** as a chiral ligand and isopropyl iodide. The adduct **5g** was obtained as a white crystalline solid in 79% yield as a mixture of two diastereomers in ratio 98:2 according to ^1H -NMR. m.p. = 134-135 °C. $[\alpha]_D = +32.1^\circ$ (c 1.0, CHCl_3) ^1H -NMR (300 MHz, CDCl_3) δ 0.75 (d, J = 6.6 Hz, 3H), 0.76 (d, J = 6.6 Hz, 3H), 0.89 (d, J =

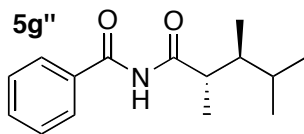
6.9 Hz, 3H), 1.12 (d, $J = 6.9$ Hz, 3H), 1.23 (s, 9H), 1.69 (dhep, $J = 6.6, 3.3$ Hz, 1H), 1.88 (dq, $J = 6.9, 6.9, 3.6$ Hz, 1H), 3.45 (dq, $J = 9.6, 6.9$ Hz, 1H), 8.06 (s, broad, 1H); ^{13}C -NMR (75 MHz, CDCl_3) δ 180.3, 177.0, 43.7, 41.1, 40.4, 27.4, 27.2, 21.8, 15.7, 15.7, 11.8. HRMS calcd. for $\text{C}_{13}\text{H}_{25}\text{NO}_2\text{Na}^+$ 250.1777 found 250.1775.



Assay of enantiomeric excess. Product enantiomeric excess was determined by two step conversion to N-(2,3,4-trimethylpentanoyl)-benzamide **5g''**. The imide **5g** was selectively methanolized,

according to the general procedure, to give 2,3,4-trimethylpentanamide **5g'** in 75% yield, as a white crystalline solid. m.p. = 143-144 °C. ^1H -NMR (400 MHz, CDCl_3) δ 0.73 (d, $J = 6.8$ Hz, 3H), 0.80 (d, $J = 6.8$ Hz, 3H), 0.92 (d, $J = 6.8$ Hz, 3H), 1.13 (d, $J = 6.8$ Hz, 3H), 1.55 (dq, $J = 9.6, 6.8, 3.6$ Hz, 1H), 1.88 (hepd, $J = 6.8, 3.6$ Hz, 1H), 2.08 (dq, $J = 9.6, 6.8$ Hz, 1H), 5.28-5.65 (m, 2H); ^{13}C -NMR (100 MHz, CDCl_3) δ 179.4, 45.2, 41.3, 27.3, 21.8, 16.3, 15.4, 11.7. HRMS calcd. for $\text{C}_8\text{H}_{18}\text{NO}^+$ 144.1382 found 144.1376.

Obtained amide **5g'** was converted to N-(2,3,4-trimethylpentanoyl)-benzamide **5g''**,

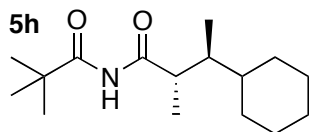


according to the general procedure for imide synthesis. The benzimide **5g''** was obtained as a white crystalline solid in 42% yield. m.p. = 163-164 °C. $[\alpha]_D = +21.3^\circ$ (c 0.8, CHCl_3). ^1H -

NMR (400 MHz, CDCl_3) δ 0.80 (d, $J = 6.8$ Hz, 3H), 0.84 (d, $J = 6.8$ Hz, 3H), 0.93 (d, $J = 6.8$ Hz, 3H), 1.22 (d, $J = 7.2$ Hz, 3H), 1.77 (dq, $J = 9.6, 6.8, 3.6$ Hz, 1H), 1.93 (hepd, $J = 6.8, 3.6$ Hz, 1H), 3.49 (dq, $J = 9.6, 6.8$ Hz, 1H), 7.48 (t, $J = 7.6$ Hz, 2H), 7.57 (t, $J = 7.2$ Hz, 1H), 7.82 (d, $J = 6.8$ Hz, 2H), 8.35 (s, broad, 1H); ^{13}C -NMR (100 MHz, CDCl_3) δ 179.8, 165.5, 133.3, 133.3, 129.1, 127.8, 44.2, 41.2, 27.4, 21.8, 15.8, 15.7, 11.9. HRMS calcd. for $\text{C}_{15}\text{H}_{21}\text{NO}_2\text{Na}^+$ 270.1464 found 270.1476.

Enantiomeric excess (92%) was determined by chiral HPLC analysis (chiralcel AD column (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.), solvent Hexanes:Isopropanol = 99:1, flow rate 0.5 mL/min; $t_{\text{r (major)}}$ = 25.0 min, $t_{\text{r (minor)}}$ = 30.0 min).

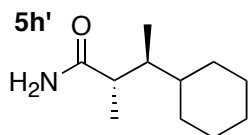
N-(3-Cyclohexyl-2-methylbutanoyl)-trimethylacetamide (5h). Prepared according to the general procedure for enantioselective alkyl radical addition reaction using MgI_2 as Lewis acid, cyclopropyl (1*S*, 2*R*)-inda-box **7** as a chiral ligand and cyclohexyl iodide. The



imide **5h** was obtained as a white crystalline solid in 62% yield as a mixture of two diastereomers in ratio 98:2 according to $^1\text{H-NMR}$. m.p. = 170-171 °C. $[\alpha]_{\text{D}} = + 24.6^\circ$ (*c* 1.0, CHCl_3).

$^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 0.82 (d, *J* = 7.0 Hz, 3H), 0.92-1.01 (m, 1H), 1.05-1.13 (m, 1H), 1.14 (d, *J* = 7.0 Hz, 3H), 1.16-1.22 (m, 2H), 1.26-1.32 (m, 1H), 1.44-1.52 (m, 2H), 1.54-1.60 (m, 1H), 1.64-1.71 (m, 2H), 1.72-1.78 (m, 2H), 3.50 (dq, *J* = 9.0, 7.0 Hz, 1H), 7.82 (s, broad, 1H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 180.2, 177.0, 43.0, 41.0, 40.4, 38.4, 32.2, 27.2, 26.9, 26.8, 26.7, 15.8, 13.3. HRMS calcd. for $\text{C}_{16}\text{H}_{29}\text{NO}_2\text{Na}^+$ 290.2090 found 290.2097.

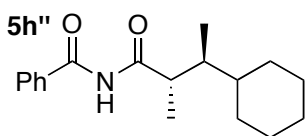
Assay of enantiomeric excess. Product enantiomeric excess was determined by two step conversion to N-(3-Cyclohexyl-2-methylbutanoyl)-benzamide **5h''**.



The imide **5h** was selectively methanolized, according to the general procedure, to give 3-cyclohexyl-2-methylbutanamide **5h'** in

92% yield, as a white crystalline solid. m.p. = 140-141 °C. $[\alpha]_{\text{D}} = + 5.7^\circ$ (*c* 1.0, CHCl_3). $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 0.84 (d, *J* = 6.5 Hz, 3H), 0.94 (qd, *J* = 12.5, 3.5 Hz, 1H), 1.14 (d, *J* = 6.5 Hz, 3H), 1.05-1.32 (m, 4H), 1.43-1.58 (m, 4H), 1.62-1.69 (m, 1H), 1.71-1.78 (m, 2H), 2.14 (dq, *J* = 9.0, 7.0 Hz, 1H), 5.30-5.60 (m, 2H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 179.6, 44.6, 41.1, 38.4, 32.3, 27.2, 26.9, 26.8, 26.4, 16.4, 13.3. HRMS calcd. for $\text{C}_{11}\text{H}_{21}\text{NONa}^+$ 206.1515 found 206.1521.

Amide **5h'** was converted to N-(2,3,4-trimethylpentanoyl)-benzimidazole **5h''**, according to the general procedure for imide synthesis. The benzimidazole **5h''** was obtained as a white



crystalline solid in 44% yield. m.p. = 135-136 °C. $[\alpha]_{\text{D}} = + 24.0^\circ$

(*c* 0.5, CHCl_3). $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 0.89 (d, *J* = 7.0 Hz, 3H), 0.99 (qd, *J* = 12.5, 3.0 Hz, 1H), 1.07-1.36 (m, 4H), 1.23 (d, *J* = 7.0 Hz, 3H), 1.46-1.56 (m, 2H), 1.58-1.70 (m, 2H), 1.72-1.80 (m, 3H), 3.56 (dq, *J* = 9.0, 7.0 Hz, 1H), 7.49 (t, *J* = 8.5 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 2H), 8.51 (s, broad, 1H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 180.0, 165.6, 133.4, 133.3, 129.1, 127.8, 43.5, 41.1, 38.5, 32.3, 27.2, 26.9, 26.8, 26.7, 15.8, 13.4. HRMS calcd. for $\text{C}_{18}\text{H}_{25}\text{NO}_2\text{Na}^+$ 310.1777 found 310.1781.

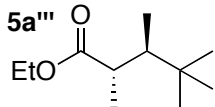
Enantiomeric excess (79%) was determined by chiral HPLC analysis (chiralcel AS column (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.), solvent

Hexanes:Isopropanol = 96:4, flow rate 0.5 mL/min; t_r (major) = 25.5 min, t_r (minor) = 31.1 min).

Determination of Relative and Absolute Stereochemistry

-Relative Stereochemistry was determined by conversion of N-(2,3,4,4-tetramethylpentanoyl)-trimethylacetamide **5c** to the known compound ethyl 2,3,4,4-tetramethylpentanoate and comparison of $J_{2,3}$ coupling constants.

2,3,4,4-Tetramethylpentamide (5a'). Prepared starting from N-(2,3,4,4-tetramethylpentanoyl)-trimethylacetamide **5c** according to the general procedure for selective imide methanolysis. The amide was obtained in 71% yield and possess the same spectra as reported earlier. ¹H-NMR (400 MHz, CDCl₃) δ 0.91 (s, 9H), 0.99 (d, J = 7.6 Hz, 3H), 1.18 (d, J = 6.8 Hz, 3H), 1.33 (qd, J = 7.2, 3.6 Hz, 1H), 2.49 (qd, J = 6.8, 3.6 Hz, 1H), 5.30-5.70 (m, 2H); ¹³C-NMR (100 MHz, CDCl₃) δ 179.1, 47.8, 41.3, 34.2, 28.3, 19.7, 11.2. HRMS calcd. for C₉H₁₉NONa⁺ 180.1358 found 180.1359.

5a' 

Ethyl 2,3,4,4-tetramethylpentanoate (5a''). 2,3,4,4-Tetramethylpentamide **5a'** (20.0 mg, 0.13 mmol) was dissolved in 2.5 mL of 75% sulfuric acid and obtained mixture was heated at 80 °C. To the hot mixture, solid sodium nitrite (70.2 mg, 1.02 mmol) was added portion wise, and then was kept at 80 °C for 30 min. The reaction was cooled at room temperature, diluted with water (5 mL) and extracted with ether (5x20 mL). The organic phase was dried with MgSO₄, filtered and evaporated to give 17.6 mg (87%) of crude 2,3,4,4-tetramethylpentanoic acid, further used without purification. The crude acid was dissolved in 1.0 mL of dichloromethane and oxalyl chloride (16.7 mg, 0.13 mmol, 11.3 μ L) was added, followed by addition of one drop of DMF. The mixture was stirred at rt for two hours and the solvent and excess of oxalyl chloride were evaporated. The residue was dissolved in 1.0 mL of absolute ethanol and obtained mixture was stirred at rt overnight. The reaction was quenched with silica gel, evaporated and purified by silica

gel chromatography to give 28 mg (62%) of ethyl 2,3,4,4-tetramethylpentanoate as oil. Spectra of obtained compound are identical to the data earlier reported in literature for *anti* diastereomer $J_{2,3} = 3.0$, lit.² $J_{2,3} = 3.1$ Hz. ¹H-NMR (500 MHz, CDCl₃) δ 0.90 (s, 9H), 0.97 (d, $J = 7.0$ Hz, 3H), 1.17 (d, $J = 7.0$ Hz, 3H), 1.25 (t, $J = 7.0$ Hz, 3H), 1.35 (qd, $J = 7.0, 3.0$ Hz, 1H), 2.75 (qd, $J = 7.0, 3.0$ Hz, 1H), 4.04-4.14 (m, 2H); ¹³C-NMR (125 MHz, CDCl₃) δ 176.6, 59.9, 48.3, 39.7, 34.1, 28.1, 19.0, 14.3, 10.6.

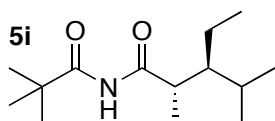
-Absolute Stereochemistry was determined by conversion of N-(2,3-dimethylpentanoyl)-trimethylacetamide to the known 2,3-dimethylpentanoic acid and comparison of optical rotations.

2,3-Dimethylpentanoic Amide (5e'). Prepared starting from major diastereomer *anti*-N-(2,3-dimethylpentanoyl)-trimethylacetamide **5e** (92% ee), according to the general procedure for selective imide methanolysis. The amide was obtained in 70% yield and possesses the same spectra as reported earlier. m.p. = 111-112 °C. $[\alpha]_D = +12.6^\circ$ (c 1.0, CHCl₃). ¹H-NMR (500 MHz, CDCl₃) δ 0.88 (t, $J = 7.5$ Hz, 3H), 0.93 (d, $J = 6.5$ Hz, 3H), 1.13 (d, $J = 7.0$ Hz, 3H), 1.11-1.20 (m, 1H), 1.53 (dq, $J = 13.5, 7.5, 4.0$ Hz, 1H), 1.58-1.65 (m, 1H), 2.10 (quin, $J = 7.0$ Hz, 1H), 5.30-5.70 (m, 2H); ¹³C-NMR (125 MHz, CDCl₃) δ 178.9, 46.2, 37.7, 25.9, 17.0, 15.1, 11.2. HRMS calcd. for C₇H₁₅NONa⁺ 152.1045 found 152.1042.

(2S, 3S)-Dimethylpentanoic Acid (5e''). Solution of *anti*-2,3-dimethylpentanoic amide **5e'** (14.8 mg, 0.114 mmol) in 2.5 mL of 75% sulfuric acid was heated at 80 °C and solid sodium nitrite (63.2 mg, 0.916 mmol) was portion wise added. The mixture was heated at 80 °C for 30 min, cooled at rt, diluted with water (5.0 mL) and extracted with ether (6 x 20 mL). The combined organics were dried with MgSO₄, filtered and evaporated to give the crude product. The crude product was purified by column chromatography using 5% ethyl acetate in hexanes and 30% ethyl acetate in hexanes, as eluents to give 11.3 mg (76%) of *anti*-dimethylpentanoic acid as oil. The optical rotation of obtained *anti*-dimethylpentanoic acid for 92% ee, is in a good agreement with earlier reported data for

2*S*, 3*S* enantiomer. $[\alpha]_D = +18.4^\circ$ (*c* 0.45, CH₂Cl₂), lit.³ $[\alpha]_D = +19.7^\circ$ (*c* 0.96, CH₂Cl₂). ¹H-NMR (500 MHz, CDCl₃) δ 0.89 (t, *J* = 7.5 Hz, 3H), 0.94 (d, *J* = 6.5 Hz, 3H), 1.14 (d, *J* = 7.0 Hz, 3H), 1.16-1.24 (m, 1H), 1.49 (dq, *J* = 13.5, 7.5, 4.5 Hz, 1H), 1.66-1.75 (m, 1H), 2.39 (quin, *J* = 7.0 Hz, 1H); ¹³C-NMR (125 MHz, CDCl₃) δ 128.4, 44.4, 37.5, 26.0, 16.8, 13.9, 11.5.

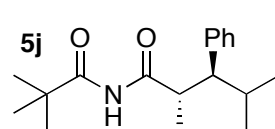
N-(3-Ethyl-2,4-dimethylpentanoyl)-trimethylacetamide (5i). Prepared according to the



general procedure for enantioselective alkyl radical addition reaction using Mg(NTf₂)₂ as Lewis acid, cyclopropyl (1*S*, 2*R*)-inda-box **7** as a chiral ligand and isopropyl iodide. The imide **5i**

was obtained as a white crystalline solid in 37% yield as a mixture of two diastereomers in ratio 95:5 according to ¹H-NMR. m.p. = 100-101 °C. $[\alpha]_D = +16.4^\circ$ (*c* 1.0, CHCl₃). ¹H-NMR (500 MHz, CDCl₃) δ 0.84 (d, *J* = 7.0 Hz, 3H); 0.91 (t, *J* = 7.5 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 1.19 (dq, *J* = 21.5, 7.5 Hz, 1H), 1.46 (ddq, *J* = 21.5, 7.5, 2.0 Hz, 1H), 1.53-1.59 (m, 1H), 1.86 (hepd, *J* = 7.0, 3.5 Hz, 1H), 3.55 (quin, *J* = 7.5 Hz, 1H), 7.89 (s, broad, 1H); ¹³C-NMR (125 MHz, CDCl₃) δ 180.1, 176.7, 47.4, 42.7, 40.4, 27.9, 27.2, 22.1, 21.4, 18.0, 14.7, 14.1. HRMS calcd. for C₁₄H₂₇NO₂Na⁺ 264.1934 found 264.1946. Enantiomeric excess (80%) was determined by chiral GC analysis (BETA DEXTM 120 Capillary Column; oven temp = 80 °C, flow rate = 14.8 mL/min, *t*_r(major) = 63.1 min, *t*_r(minor) = 62.1 min).

N-(2,4-Dimethyl-3-Phenylpentanoyl)-trimethylacetamide (5j). Obtained according to

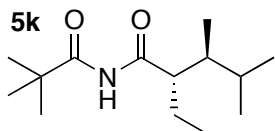


the general procedure for enantioselective alkyl radical addition reaction using Mg(NTf₂)₂ as Lewis acid, cyclopropyl (1*S*, 2*R*)-inda-box **7** as a chiral ligand and isopropyl iodide. The imide **5j**

was obtained as a white crystalline solid in 71% yield as a mixture of two diastereomers in ratio 99:1 according to ¹H-NMR. m.p. = 159-160 °C. $[\alpha]_D = -28.9^\circ$ (*c* 1.0, CHCl₃). ¹H-NMR (400 MHz, CDCl₃) δ 0.74 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 7.2 Hz, 3H), 1.09 (s, 9H), 1.27 (d, *J* = 6.8 Hz, 3H), 2.14 (hepd, *J* = 6.8, 4.0 Hz, 1H), 2.88 (dd, *J* = 11.2, 4.0 Hz, 1H), 4.23 (dq, *J* = 11.2, 6.8 Hz, 1H), 7.07-7.20 (m, 5H), 7.53 (s, broad, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 179.3, 177.0, 140.4, 129.7, 127.8, 126.4, 53.8, 41.9, 40.3, 27.6,

27.1, 22.0, 16.4, 16.2. HRMS calcd. for $C_{18}H_{27}NO_2Na^+$ 312.1934 found 312.1930. Enantiomeric excess (93%) was determined by chiral HPLC analysis (two connected chiralcel OD columns (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.), solvent Hexanes:Isopropanol = 99:1, flow rate 0.5 mL/min; $t_{r(\text{major})}$ = 21.9 min, $t_{r(\text{minor})}$ = 37.9 min).

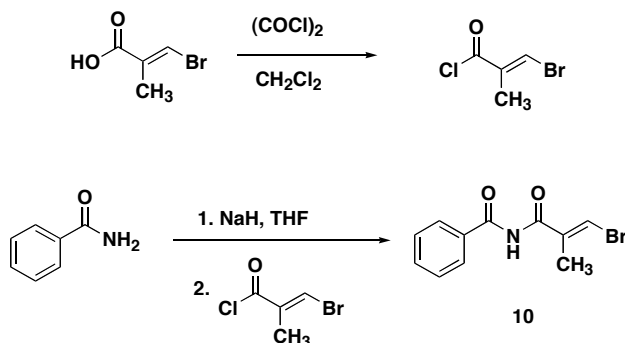
N-(2-Ethyl-3,4-dimethylpentanoyl)-trimethylacetamide (5k). Prepared according to



the general procedure for enantioselective alkyl radical addition reaction using $Mg(NTf_2)_2$ as Lewis acid, cyclopropyl (1*S*, 2*R*)-inda-box **7** as a chiral ligand and isopropyl iodide. The imide **5k**

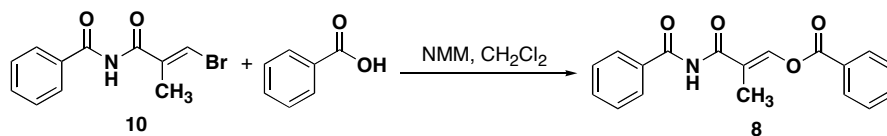
was obtained as a white crystalline solid in 50% yield as a mixture of two diastereomers in ratio 87:13 according to 1H -NMR. m.p. = 121-122 °C. $[\alpha]_D = +4.0^\circ$ (c 1.0, $CHCl_3$). 1H -NMR (500 MHz, $CDCl_3$) δ 0.79 (d, J = 6.5 Hz, 6H), 0.87 (t, J = 7.5 Hz, 3H), 0.91 (d, J = 7.0, 3H), 1.24 (s, 9H), 1.58-1.66 (m, 2H), 1.67-1.74 (m, 1H), 1.86 (hepd, J = 7.0, 3.5 Hz, 1H), 3.47 (td, J = 9.5, 4.5 Hz, 1H), 7.93 (s, broad, 1H); ^{13}C -NMR (125 MHz, $CDCl_3$) δ 179.2, 176.8, 50.2, 40.4, 40.3, 27.8, 27.2, 23.4, 21.8, 16.0, 11.6, 11.4. HRMS calcd. for $C_{14}H_{27}NO_2Na^+$ 264.1933 found 264.1935. Enantiomeric excess (74%) was determined by chiral GC analysis (BETA DEXTM 120 Capillary Column; oven temp = 90 °C, flow rate = 14.8 mL/min, $t_{r(\text{major})}$ = 28.5 min, $t_{r(\text{minor})}$ = 26.9 min).

General procedure for the preparation of propionate aldol starting material. Under N_2 , to a flask containing 3-bromomethacrylic acid⁵ (7.7 g, 47 mmol), was added oxalyl chloride (4.1 mL, 52 mmol) dropwise. After complete addition, 3-5 drops of DMF was added and the reaction was allowed to stir at room temperature for three hours.



To another flask containing benzamide (7.3 g, 60 mmol) and THF (160 mL), was added NaH (60% in mineral oil, 3.6 g, 90 mmol) in portions at 0 °C under N₂. After complete addition, the solution was stirred for 0.5 hour at 0 °C and then for one hour at room temperature. A solution of 3-bromomethacryloyl chloride (taken directly from the previous reaction) was added via syringe at room temperature and the mixture stirred for 4 hours. The reaction was quenched with approximately 5 mL of water and the THF was removed using a rotary evaporator. The concentrated mixture was then extracted with EtOAc (3 x 60 mL). The extracts were combined, washed with water (2 x 20 mL) and 1 M NaOH (2 x 20 mL), dried over MgSO₄ and concentrated. The crude product was purified by chromatography on silica gel using hexane/EtOAc (5:1) as eluent to yield 6.0 g of **10** (48%) as a white solid; mp: 139-142 °C. ¹H NMR (CDCl₃, 500 MHz) δ 2.10 (d, *J* = 1.5 Hz, 3 H), 7.28 (d, *J* = 1.5 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 2H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 2H), 8.67 (bs, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 16.7, 120.0, 128.1, 129.2, 133.1, 133.5, 138.0, 166.19, 166.20. HRMS Exact mass calcd for C₁₁H₁₀BrNO₂Na [M + Na]⁺: 289.9787; Found: 289.9787.

Synthesis of **8**.

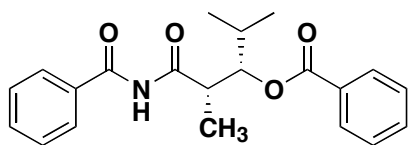


Under N₂, to a flask containing **10** (2.0 g, 7.5 mmol) and benzoic acid (1.1 g, 9.0 mmol) in 15 mL of methylene chloride, was added N-methylmorpholine (NMM) (1.7 mL, 15 mmol) via syringe. The reaction was stirred for 48 hours at room temperature. The reaction was then washed with water (2 x 10 mL) and 1 M NaOH (2 x 10 mL), dried over MgSO₄ and concentrated. The crude product was purified by chromatography on silica gel using hexane/EtOAc (3:1) as eluent to yield 1.5 g of **8**. 65% yield; mp: 173-175 °C; ¹H NMR (CDCl₃, 500 MHz) δ 2.13 (d, *J* = 1.5 Hz, 3H), 7.48-7.55 (m, 4H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 2H), 8.14 (d, *J* = 8.0 Hz, 2H), 8.37 (d, *J* = 1.5 Hz, 1H), 8.57 (bs, 1H) ¹³C NMR (CDCl₃, 125 MHz) δ 11.1, 117.8, 128.1,

128.2, 129.06, 129.09, 130.5, 133.3, 133.5, 135.7, 142.9, 162.7, 166.5, 167.2; HRMS Exact mass calcd for $C_{18}H_{15}NO_4Na$ $[M + Na]^+$: 332.0893; Found: 332.0892.

Representative experimental procedure for chiral Lewis acid catalyzed conjugate addition of radicals to alkoxy enoates. Under N_2 , a mixture of Lewis acid (0.045 mmol) and ligand (0.045 mmol) in CH_2Cl_2 (1.5 mL) was stirred at rt for 45 min. Imide (**8**) (0.15 mmol) (dissolved in 1 mL CH_2Cl_2) was added and the mixture was allowed to stir for an additional 30 min and then cooled to $-78\text{ }^\circ\text{C}$. The reaction was then initiated by sequential addition of 2-iodo propane (or other radical precursors = RX) (1.5 mmol), $n\text{-Bu}_3\text{SnH}$ (0.45 mmol), Et_3B (0.45 mmol 1 M solution in hexanes) and oxygen (introduced via syringe). The reaction was monitored by TLC (30% EtOAc in hexane) and when judged complete was quenched with silica gel, concentrated, washed with hexanes and extracted with ether. The ether extract was concentrated over silica gel and purified by silica gel chromatography (hexane-ethyl acetate) to give the products (**9a-c**). The reaction procedure for standard racemic reactions is the same as above with the following modification. Racemic standards were prepared using $Yb(OTf)_3$ as a Lewis acid in the absence of a chiral ligand and methylene chloride:tetrahydrofuran (2:1) as a solvent.

(9a): Benzoic acid 3-benzoylamino-1-isopropyl-2-methyl-3-oxo-propyl ester: 42 mg, 80 % yield (white solid); mp: 153-156 $^\circ\text{C}$; The enantiomeric purity was determined by

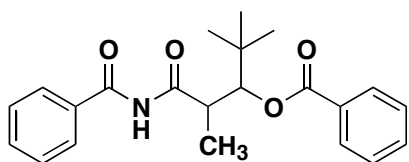


9a: $C_{21}H_{23}NO_4$
Mol. Wt.: 353.4116

HPLC (254 nm, $25\text{ }^\circ\text{C}$) t_R 19.1 min (major); t_R 26.7 min (minor) [Chiralcel AS (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 93/7, 0.7 mL/min] as 82% ee. $[\alpha] = +2.20^\circ$ (c 1.0, $CHCl_3$); Diastereomeric ratio (determined by 500 MHz 1H NMR): 99:1; 1H

NMR ($CDCl_3$, 500 MHz) δ 1.04 (dd, $J = 23.5$ and 7.0 Hz, 6H), 1.31 (d, $J = 7.0$ Hz, 3H), 2.12-2.22 (m, 1H), 4.05-4.15 (m, 1H), 5.40 (dd, $J = 8.0$ and 4.0 Hz, 1H), 7.33 (t, $J = 8.0$ Hz, 2H), 7.42 (t, $J = 8.0$ Hz, 2H), 7.49 (t, $J = 7.5$ Hz, 1H), 7.56 (t, $J = 7.5$ Hz, 1H), 7.74 (d, $J = 7.5$ Hz, 2H), 7.99 (d, $J = 7.5$ Hz, 2H), 8.75 (bs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.2, 16.5, 20.0, 29.7, 43.0, 79.7, 127.9, 128.6, 129.1, 129.9, 130.2, 133.1, 133.2, 133.3,

165.7, 166.2, 176.3; HRMS Exact mass calcd for $C_{21}H_{23}NO_4Na$ $[M + Na]^+$: 376.1519; Found: 376.1519.

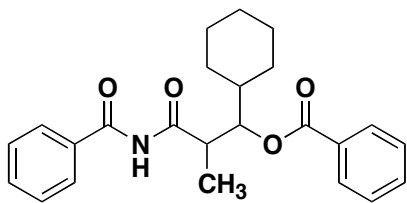


9b: $C_{22}H_{25}NO_4$
Mol. Wt.: 367.4382

(9b): Benzoic acid 3-benzoylamino-1-tert-butyl-2-methyl-3-oxo-propyl ester: 32 mg, 60% yield (white solid); mp: 131-133 °C; The enantiomeric purity was determined by HPLC (254 nm, 25 °C) t_R 20.1 min (major); t_R 29.1 min (minor) [Chiralcel AS (0.46 cm x

25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 93/7, 0.7 mL/min] as 90% ee. $[\alpha] = -10.0^\circ$ (c 1.0, $CHCl_3$); Diastereomeric ratio (determined by 500 MHz 1H NMR): 99:1; 1H NMR ($CDCl_3$, 500 MHz) δ 1.09 (s, 9H), 1.40 (d, $J = 7.0$ Hz, 3H), 3.84-3.93 (m, 1H), 5.22 (d, $J = 5.0$ Hz, 1H), 7.35-7.43 (m, 4H), 7.52-7.59 (m, 2H), 7.73 (d, $J = 7.5$ Hz, 2H), 8.03 (d, $J = 7.0$ Hz, 2H), 8.72 (bs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.3, 27.0, 36.3, 42.7, 82.8, 127.8, 127.9, 128.8, 129.1, 130.0, 133.29, 133.32, 133.5, 165.5, 166.2, 175.0; HRMS Exact mass calcd for $C_{22}H_{25}NO_4Na$ $[M + Na]^+$: 390.1676; Found: 390.1660.

(9c): Benzoic acid 3-benzoylamino-1-cyclohexyl-2-methyl-3-oxo-propyl ester: 38 mg, 64% yield (white solid); mp: 169-172 °C; The enantiomeric purity was determined by



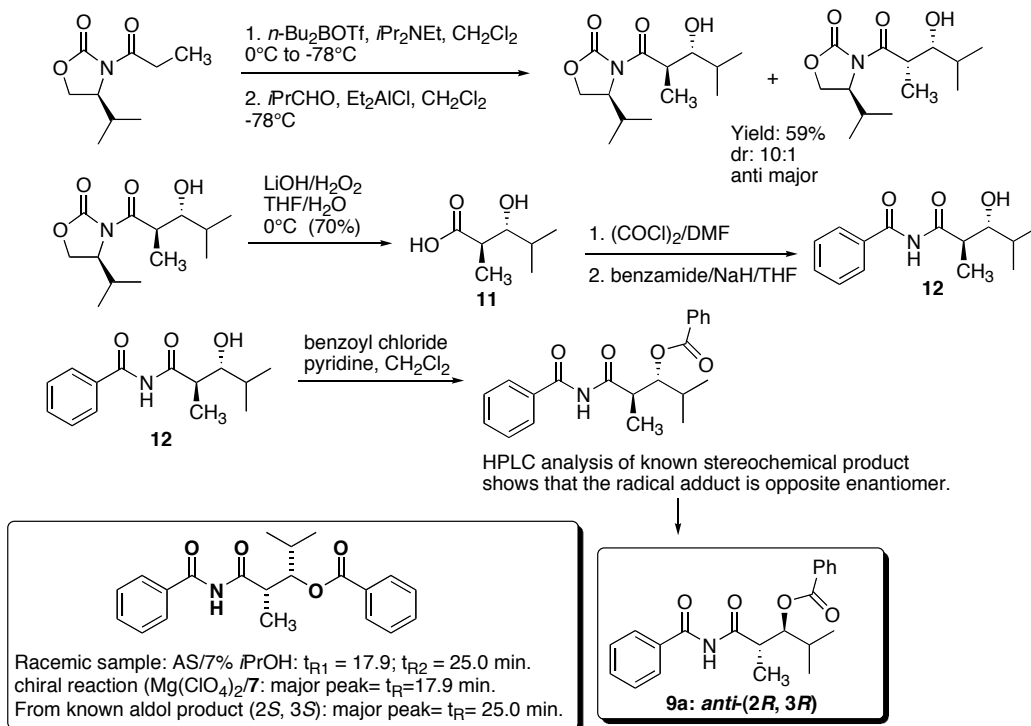
9c: $C_{24}H_{27}NO_4$
Mol. Wt.: 393.4755

HPLC (254 nm, 25 °C) t_R 17.8 min (major); t_R 27.8 min (minor) [Chiralcel AS (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 93/7, 0.7 mL/min] as 70% ee. $[\alpha] = +3.0^\circ$ (c 0.5, $CHCl_3$); Diastereomeric ratio (determined by 500 MHz 1H NMR): 99:1; 1H NMR ($CDCl_3$, 500 MHz) δ 1.06-1.30

(m, 6H), 1.32 (d, $J = 7.0$ Hz, 3H), 1.60-1.92 (m, 5H), 4.02-4.12 (m, 1H), 5.37 (dd, $J = 8.0$ and 5.0 Hz, 1H), 7.35 (t, $J = 7.5$ Hz, 2H), 7.43 (t, $J = 7.5$ Hz, 2H), 7.51 (t, $J = 7.5$ Hz, 1H), 7.57 (t, $J = 7.5$ Hz, 1H), 7.75 (d, $J = 7.0$ Hz, 2H), 8.01 (d, $J = 7.0$ Hz, 2H), 8.66 (bs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.2, 26.2, 26.37, 26.42, 27.1, 30.4, 39.5, 42.5, 79.4, 127.8, 128.6, 129.1, 129.9, 130.2, 133.16, 133.24, 133.3, 165.6, 166.2, 176.0; HRMS Exact mass calcd for $C_{24}H_{27}NO_4Na$ $[M + Na]^+$: 416.1832; Found: 416.1838.

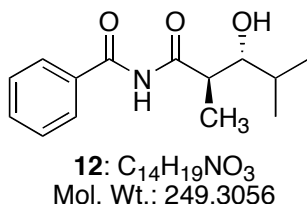
Stereochemical analysis:

The relative and absolute stereochemistry was assigned by converting known acid (**11**)⁶ into the radical product (**9a**). It was found that the product from the propionate aldol radical reaction (**9a**) contained *anti*-(2*S*,3*S*) stereochemistry (see below).



Under N₂, to a flask containing (2*R*,3*R*)-3-Hydroxy-2,4-dimethylpentanoic acid⁶ (**11**) (190 mg, 1.3 mmol), was added oxalyl chloride (0.18 mL, 0.20 mmol). After complete addition, 1 drop of DMF was added and the reaction was allowed to stir at room temperature for three hours.

To another flask containing benzamide (315 mg, 2.6 mmol) and THF (5 mL), was added *n*-BuLi (2.5 M in hexanes; 1.1 mL, 2.9 mmol) 0 °C under N₂.



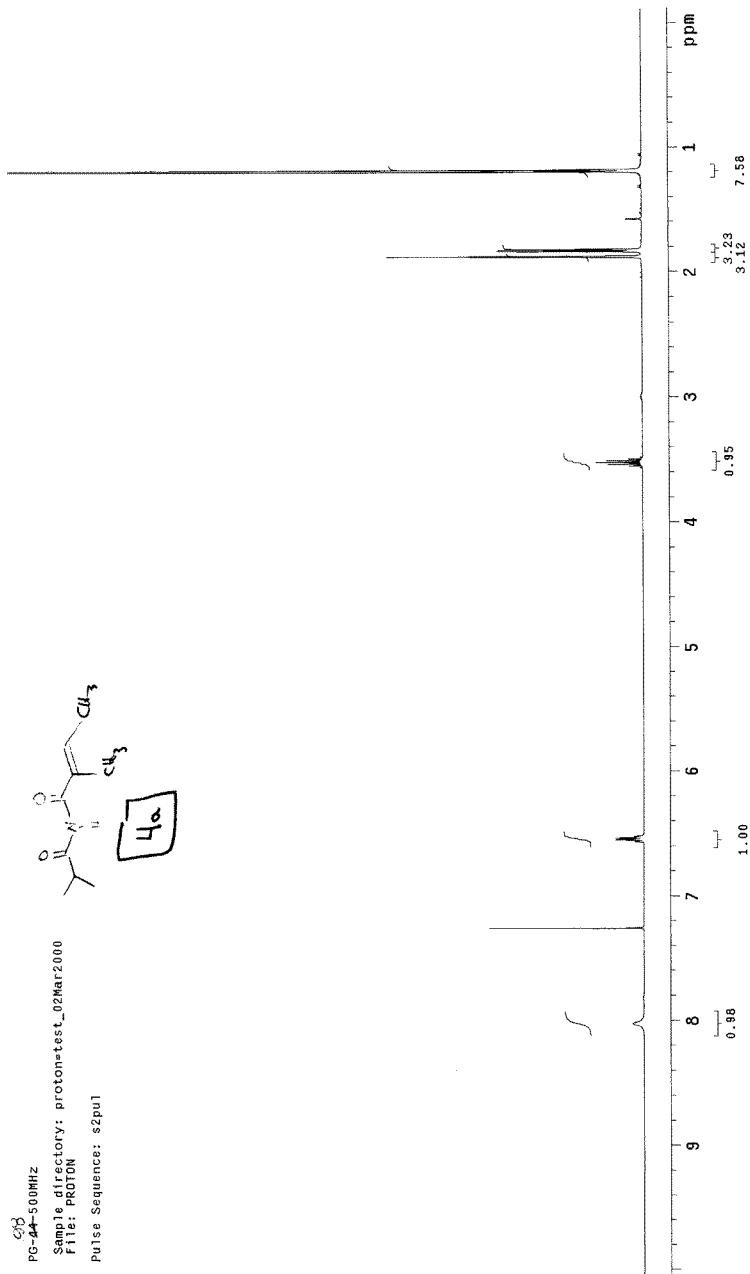
After complete addition, the solution was stirred for 0.5 hour at 0 °C and then for one hour at room temperature. A solution (2*R*,3*R*)-3-Hydroxy-2,4-dimethylpentanoyl chloride (taken directly from the previous reaction) was added via syringe at

room temperature and the mixture stirred for 2 hours. The reaction was quenched and the

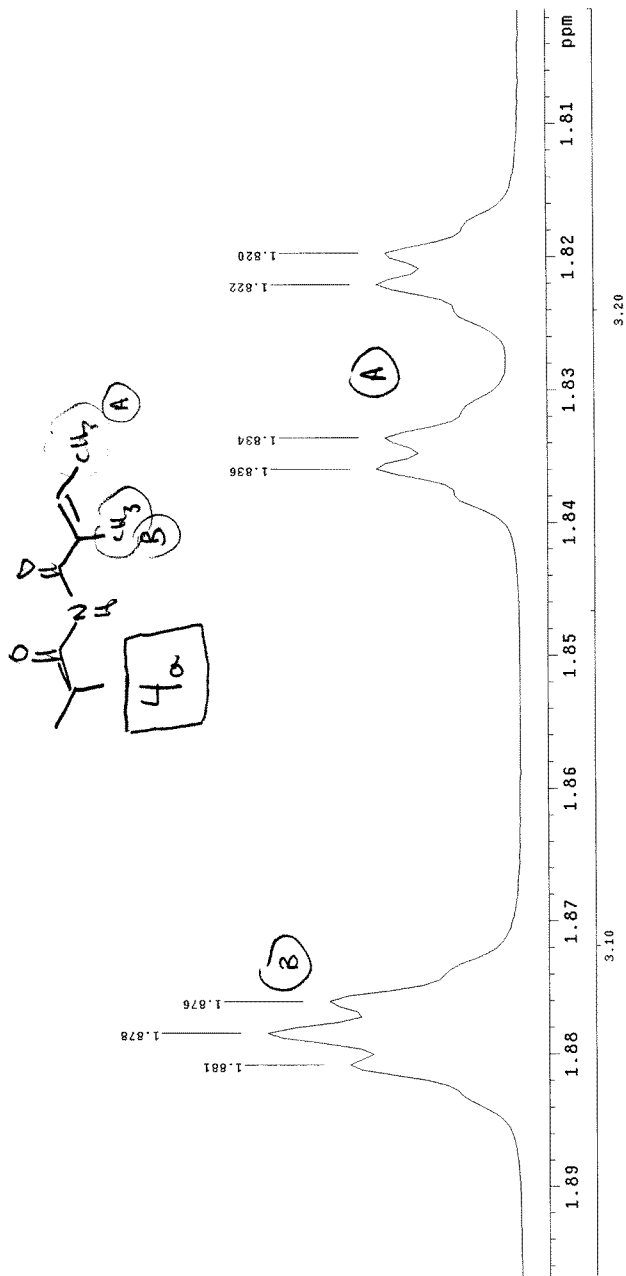
THF was removed using a rotary evaporator. The crude product was purified by chromatography on silica gel using hexane/EtOAc (1:1 to 0:1) as eluent to yield 222 mg of *anti*-(2*R*,3*R*)-**12** (68%). ¹H NMR (CDCl₃, 500 MHz) δ 1.00 (dd, *J* = 11.2 and 6.5 Hz, 6H), 1.23 (d, *J* = 6.5 Hz, 3H), 2.07-2.17 (m, 1H), 2.82 (q, *J* = 7.0 Hz, 1H), 5.17-5.20 (m, 1H), 5.50 (bs, 1H), 5.78 (bs, 1H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 14.9, 17.2, 19.8, 30.0, 43.9, 79.9, 127.6, 128.8, 129.8, 133.4, 166.4, 176.1. HRMS Exact mass calcd for C₁₄H₁₉NO₃Na [M + Na]⁺: 272.1263; Found: 272.1285. Next, **12** (220 mg, 0.9 mmol) was converted to *enant*-**9a** by adding benzoyl chloride (140 mg, 1.0 mmol) and pyridine (1.5 mmol) to a solution of **12** in methylene chloride (10 mL) at room temperature. The crude product was purified by chromatography on silica gel using hexane/EtOAc (3:1) as eluent to yield 160 mg of the enantiomer of **9a** (50%).

References:

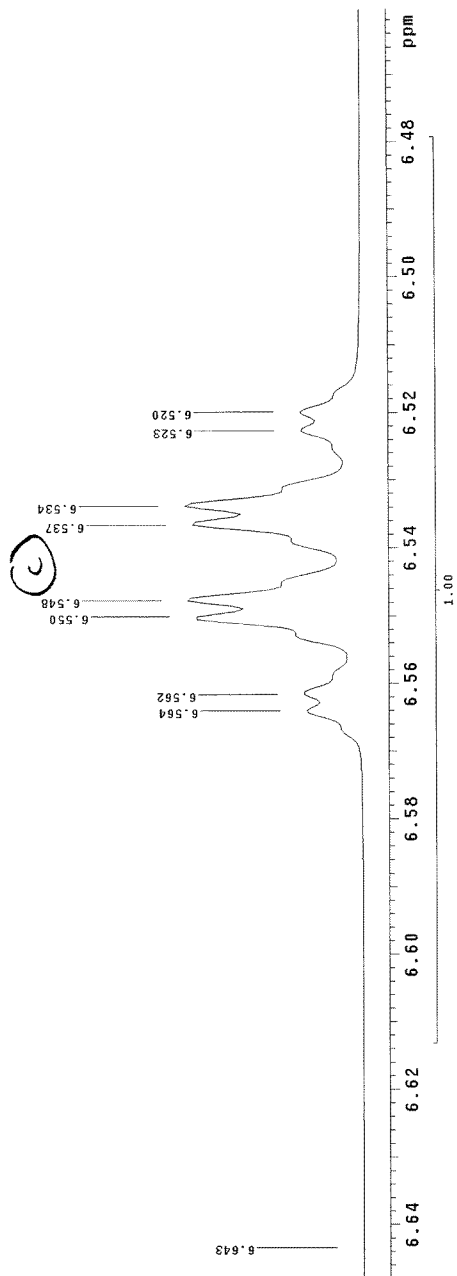
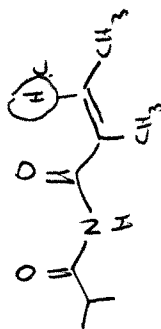
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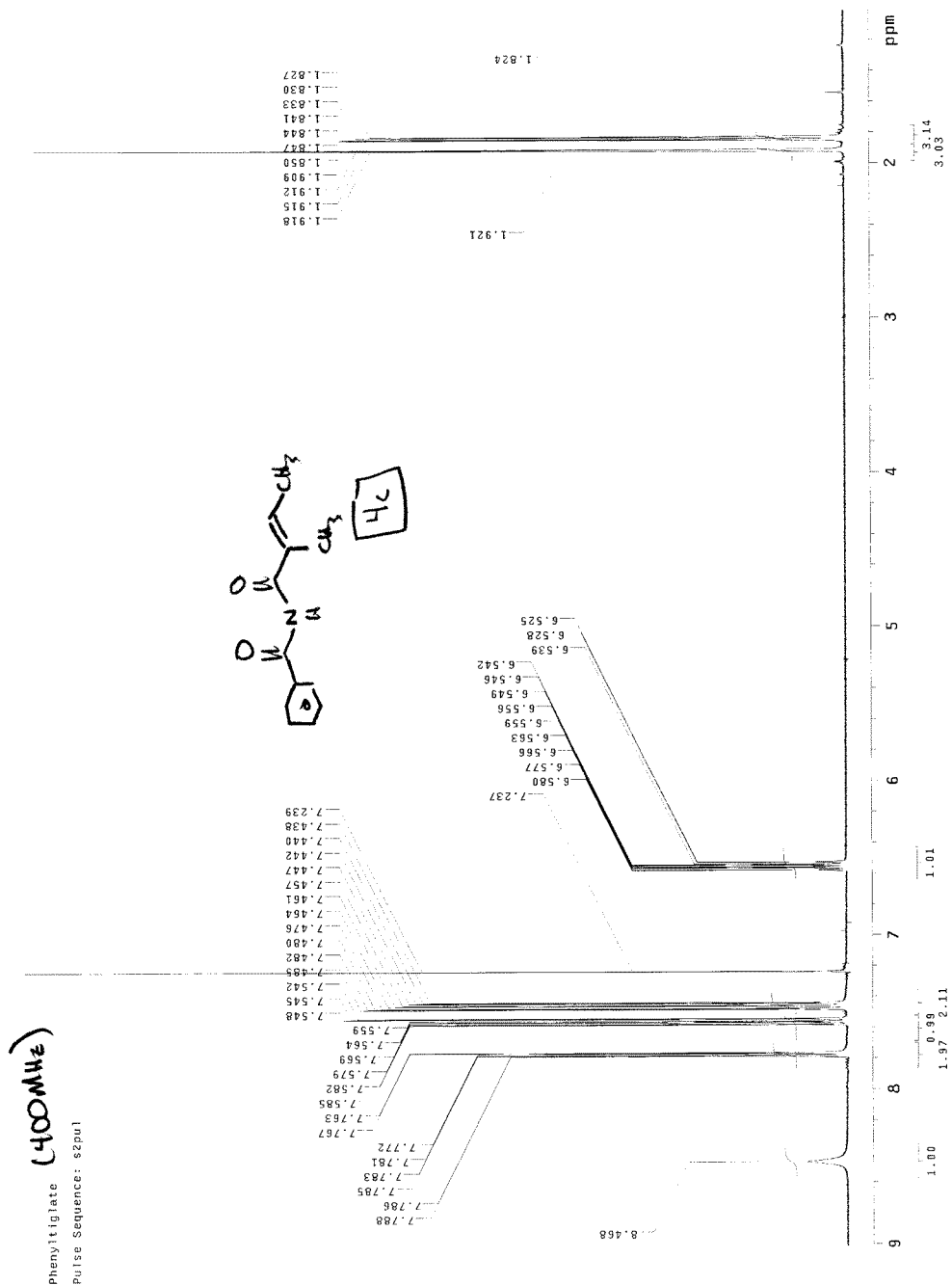


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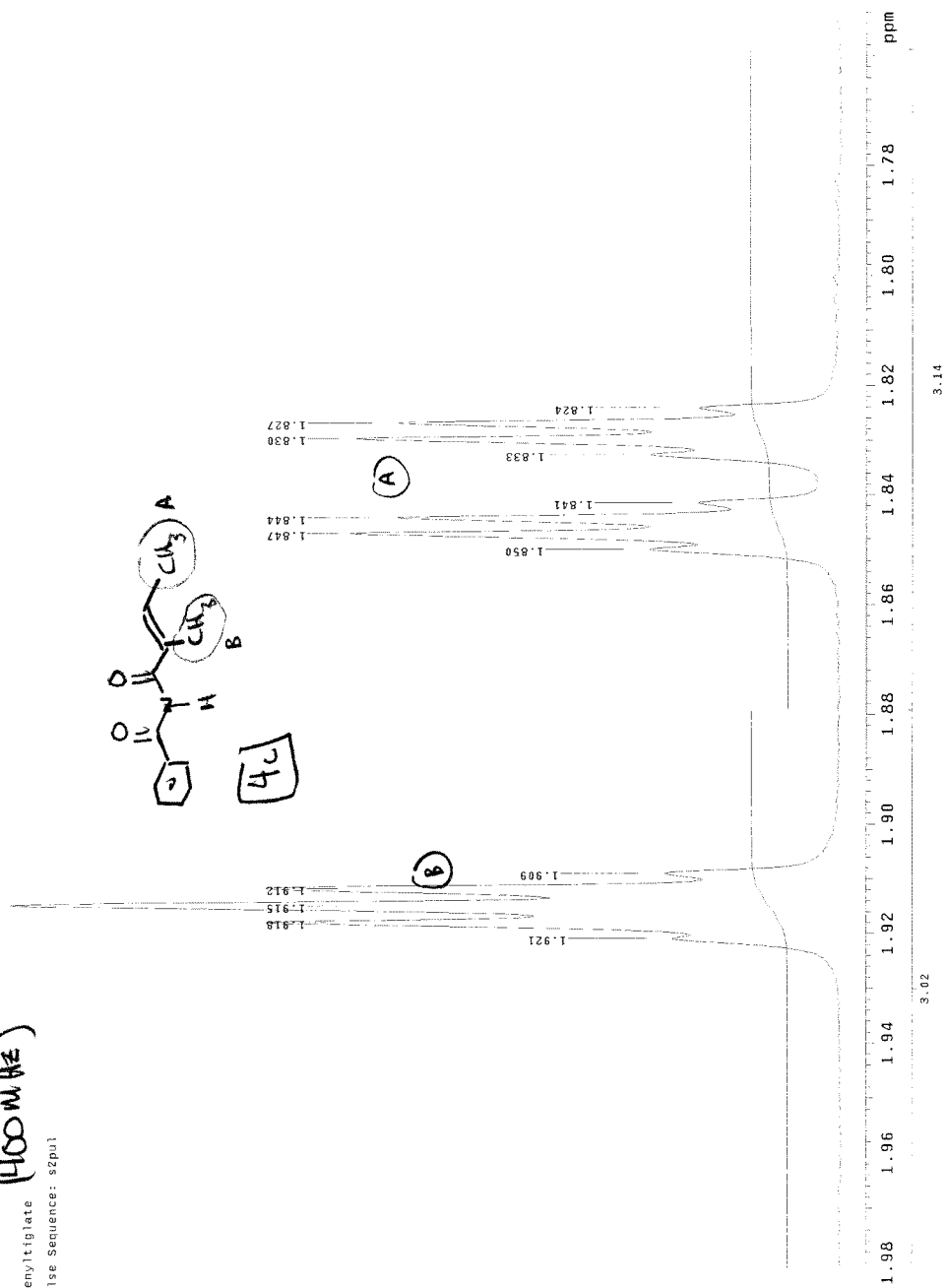


38
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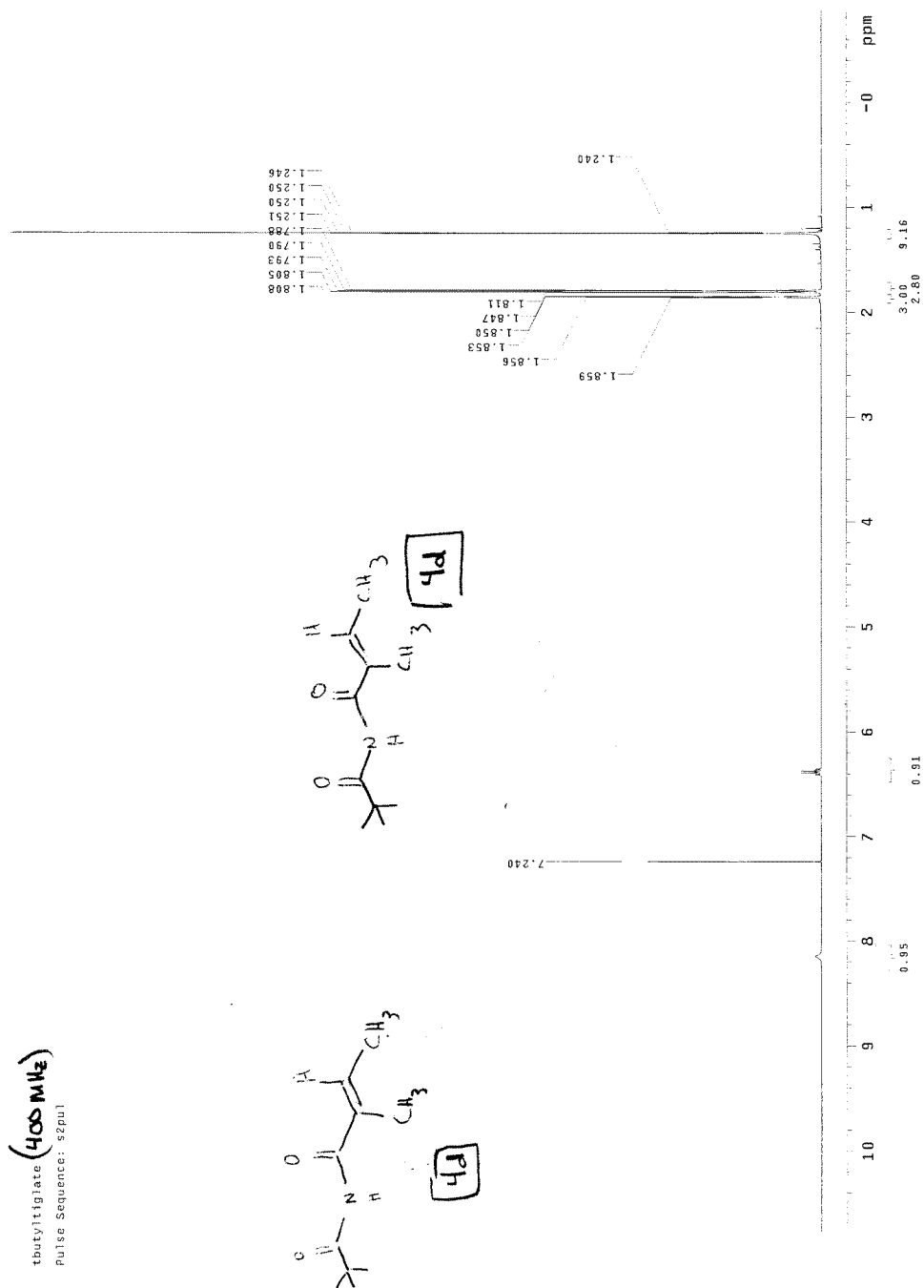




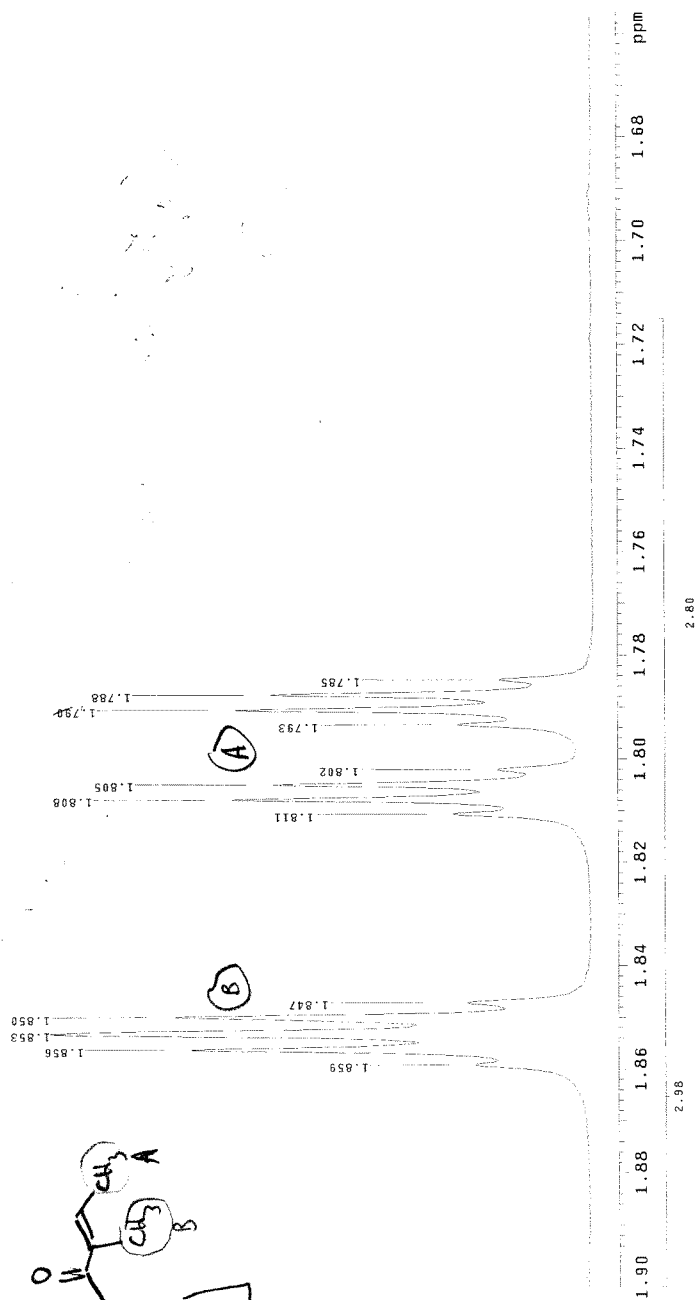
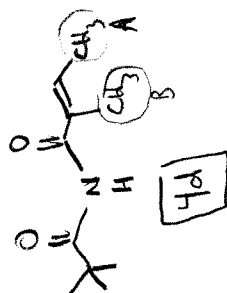
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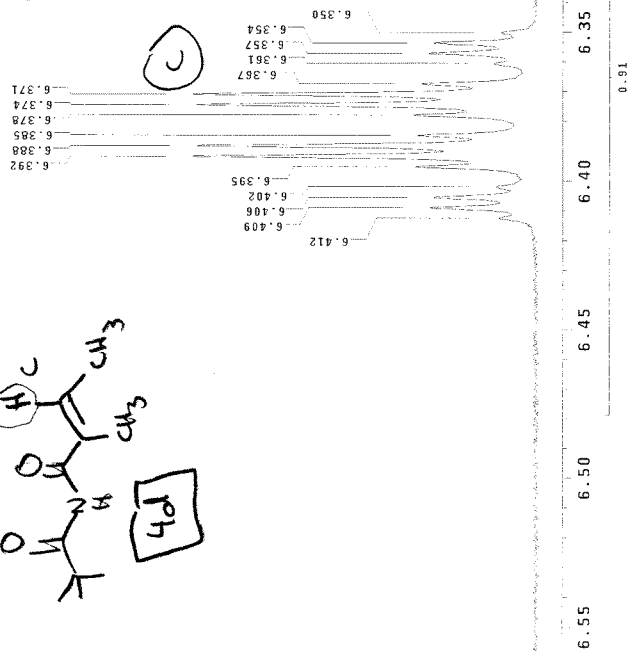
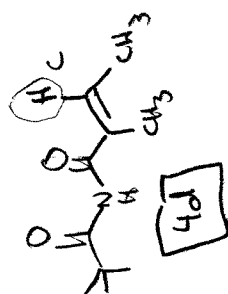
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thuty'tiglate (400 MHz)
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tbutyitiglate (400 MHz)
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2D Width 4600.1 Hz
15 4600.1 Hz

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2 x 356 increments

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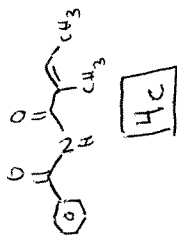
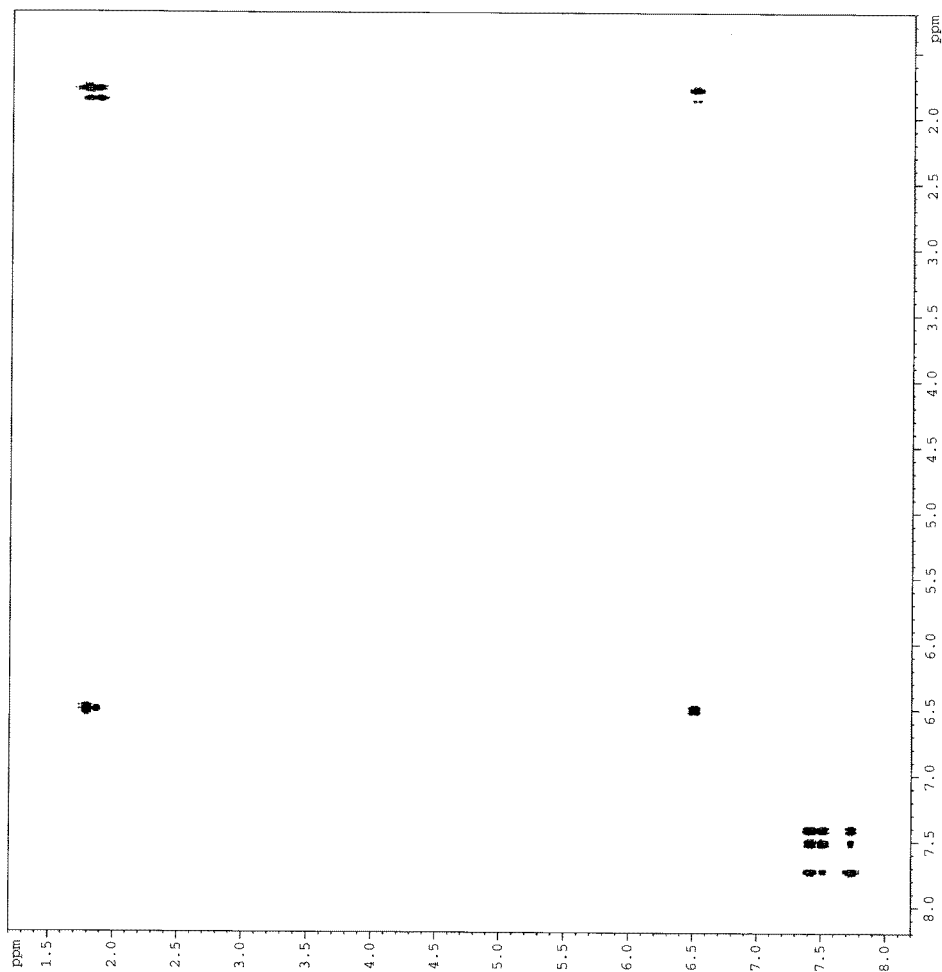
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total time 4 hr, 41 min,

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Sample directory: proton-test_02Mar2000
File: PROTON

Pulse Sequence: gDQCOSY

Solvent: CDCl3

Temp.: 25.0 C / 298.1 K

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OBSERVE H1Drems

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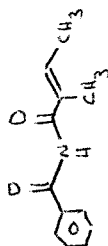
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4c

EXPANSIONS

