Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

for

Angew. Chem. Int. Ed. Z50699

69451 Weinheim, Germany

Cu-Catalyzed Enantioselective Conjugate Additions of Alkylzincs to Unsaturated N-Acyloxazolidinones Promoted by a Chiral Triamide Phosphine

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General. Infrared (IR) spectra are recorded on a Perkin Elmer 781 spectrophotometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m) or weak (w). ^{1}H NMR spectra are recorded on a Varian Unity INOVA 400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance resulting from incomplete deuteration as the internal standard ($CDCl_3$: 7.26). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants, and assignment. ^{13}C NMR spectra are recorded on a Varian Unity INOVA 400 (100 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: 77.16). Enantiomer ratios are determined by chiral GLC analysis; (Alltech Associates Chiraldex GTA column (30 m x 0.25 mm) or Supelco Betadex 120 column (30 m x 0.25 mm)), or by chiral HPLC analysis (Chiral Technologies Chiralpak OD column (0.46 cm x 25 cm)) in comparison with authentic racemic materials. Elemental analyses are performed by Robertson Microlit Laboratories (Madison, New Jersey). High resolution mass spectrometry is performed by the University of Illinois Mass Spectrometry Laboratories (Urbana, Illinois) and by Mr. Chris Kowalczyk (on a Micromass LCT ESI-MS (positive mode) at the Mass Spectrometry Facility, Boston College). Optical rotation values are recorded on a Rudolph Research Analytical Autopol IV polarimeter.

Unless otherwise stated, all reactions are conducted in oven- (135 °C) and flame-dried glassware under an inert atmosphere of nitrogen. Solvents are purified under a positive pressure of dry argon by a modified Advanced ChemTech purification system – toluene is purified through Cu and alumina columns, dichloromethane and THF are purified through two alumina columns. Diethylzinc and dimethylzinc are purchased from Strem and used without purification. Other alkylzincs are prepared using known methods.[1] Copper (I) triflate (benzene complex, 2:1) is prepared according to a published procedure,[2] while copper (I) triflate (toluene complex, 2:1) is purchased from Aldrich and used without purification. Unless otherwise stated, substrates are synthesized from commercially available starting materials using known methods. EDC•HCl, HOBt•H_2O, piperidine, butylamine, Boc- and Fmoc-protected amino acids and 2-(diphenylphosphino)benzoic acid are purchased from commercial sources and used without further purification. Wang resin (1.1 mmol/g) is purchased from Novabiochem. Propenoyl chloride is purchased from Aldrich and distilled prior to use. 2-Oxazolidinone is purchased from Aldrich and recrystallized from benzene before use.

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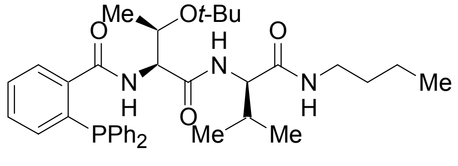
[1] P. Knochel, R. Singer, *Chem. Rev.* **1993**, *93*, 2117-2188 and references cited therein.

[2] (a) R. G. Salomon, J. K. Kochi, *J. Am. Chem. Soc.* **1973**, *95*, 1889-1897. (b) R. G. Salomon, J. K. Kochi, *J. Am. Chem. Soc.* **1973**, *95*, 3300-3310.



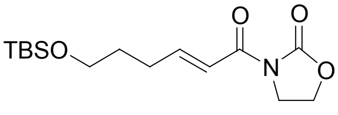
4

2-(Diphenylphosphino)benzoic-L-Thr(But)-D-Val-NHBu (4): Boc-D-Val-OH (1.30 g, 5.98 mmol) is dissolved in 40 mL of CH_2Cl_2, and HOBt•H_2O (0.916 g, 5.98 mmol), EDC•HCl (1.14 g, 5.98 mmol) and butyl amine (1.24 mL, 12.6 mmol) are added successively at 22 °C. The resulting solution is stirred at 22 °C for 4 h at which time TLC analysis shows absence of starting material (12:1 CH_2Cl_2/ MeOH; R_f starting material = 0.7, R_f product = 0.8). 40 mL of a 10 wt. % aqueous solution of citric acid is then added and the two layers are separated. The organic layer is washed twice each with 40 mL of 10 wt. % aqueous citric acid and 40 mL of saturated aqueous $NaHCO_3$, followed by 40 mL of saturated NaCl. The organic layer is then dried over $MgSO_4$ before concentrating to a yellow oil (1.47 g, 5.41 mmol, 90%). The product is identified by ^{1}H NMR before Boc deprotection.

2 mL of trifluoroacetic acid is added dropwise to Boc-D-Val-NHBu (0.459 g, 1.69 mmol) at 0 °C. The solution is allowed to warm to room temperature and is stirred for 30 min. At this time, the reaction is cooled back to 0 °C before quenching by dropwise addition of a 6N aqueous solution of NaOH until pH >10. The aqueous solution is then washed with CH_2Cl_2 (3 x 20 mL). The combined organic extracts are dried over $MgSO_4$ and concentrated to afford H_2N-D-Val-NHBu (0.252 g, 1.46 mmol, 87%). The product is identified solely by ^{1}H NMR before proceeding to the next amide coupling reaction.

Fmoc-L-Thr(But)-OH (0.501 g, 1.26 mmol) is dissolved in 10 mL CH_2Cl_2 and HOBt•H_2O (0.193 g, 1.26 mmol), EDC•HCl (0.241 g, 1.26 mmol) and a solution of H_2N-D-Val-NHBu (0.217 g, 1.26 mmol) in 10 mL CH_2Cl_2 are successively added at 22 °C. The resulting solution is stirred at 22 °C for 4 h before quenching and extracting as above. The resulting oil is identified by ^{1}H NMR before Fmoc deprotection. Fmoc-L-Thr(But)-D-Val-NHBu is dissolved in 10 mL CH_2Cl_2 and piperidine (498 µL, 5.03 mmol) is added at 22 °C. The reaction is monitored by TLC until starting material is completely consumed (200:9:1 EtOAc/MeOH/concentrated aqueous NH_4OH; R_f starting material = 0.5, R_f product = 0.2). The reaction is then concentrated and the resulting solid purified by silica gel column chromatography (1:1 hexanes/EtOAc to 100:9:1 EtOAc/MeOH:concentrated aqueous NH_4OH) to yield a yellow oil (0.337 g, 0.981 mmol, 78% over 2 steps). This amine is identified by ^{1}H NMR before the final coupling.

2-(Diphenylphosphino)benzoic acid (0.301 g, 0.981 mmol) is dissolved in 5 mL of CH_2Cl_2 and HOBt•H_2O (0.150 g, 0.981 mmol), EDC•HCl (0.188 g, 0.981 mmol) and a solution of H_2N-L-Thr(But)-D-Val-NHBu (0.337 g, 0.981 mmol) in 5 mL CH_2Cl_2 are successively added at 22 °C. The resulting solution is stirred for 12 h before the addition of 15 mL of a 10 wt. % solution of citric acid and then extraction by the usual procedure. The crude is purified either by recrystallization (hexanes/EtOAc, 0.400 g, 0.647 mmol, 66%) or by silica gel chromatography (2:1 EtOAc/hexanes, R_f product = 0.2, 73% yield) to yield a white crystalline solid. IR (solid film): 3322 (m), 2968 (m), 2930 (w), 2868 (w), 1640 (s), 1520 (s), 1463 (w), 1432 (w); ^{1}H NMR (400 MHz): δ 7.60 (1H, ddd, *J* = 14.0, 7.4, 3.6 Hz, Ar**H**), 7.46 (1H, d, *J* = 8.0 Hz, Ar**H** or N**H**), 7.37 (1H, ddd, *J* = 7.4, 7.4, 1.5 Hz, Ar**H**), 7.32 (11H, m, Ar**H** or N**H**), 7.01 (1H, d, *J* = 5.9 Hz, Ar**H** or N**H**), 6.95 (1H, ddd, *J* = 7.6, 4.2, 1.0 Hz, Ar**H** or N**H**), 5.92 (1H, dd, *J* = 5.8 Hz, N**H**), 4.39 (1H, dd, *J* = 6.0, 3.8 Hz, NC**H**CO), 4.13 (1H, m, NC**H**CO), 3.87 (1H, m, C**H**O) 3.25 (2H, m, NC**H**$_2$), 2.28 (1H, m, C**H**Me$_2$), 1.48 (2H, m, C**H**$_2$), 1.33 (2H, m, C**H**$_2$), 1.20 (9H, s, *t*-**Bu**), 0.98 (3H, d, *J* = 6.9 Hz, C**H**$_3$), 0.94 (3H, d, *J* = 6.9 Hz, C**H**$_3$), 0.91 (3H, t, *J* = 7.4 Hz, C**H**$_3$), 0.90 (3H, d, 7.1 Hz, C**H**$_3$); ^{13}C NMR (100 MHz): δ 170.6, 170.0, 168.8, 140.5, 140.3, 137.3, 137.2, 137.2, 137.0, 137.0, 136.8, 134.4, 134.2, 134.1, 133.8, 130.5, 128.9, 128.9, 128.7, 128.7, 128.6, 128.6, 127.7, 127.7, 75.6, 66.3, 59.5, 58.2, 39.3, 31.8, 30.2, 28.3, 20.2, 19.7, 18.0, 18.0, 13.8; Anal Calcd for $C_{36}H_{48}N_3O_4P$: C, 69.99; H, 7.83; Found: C, 69.75; H, 7.77; $[\alpha]_D^{20}$ +7.7° (*c* = 1.3, $CHCl_3$).



5c

3-[6-(*tert*-Butyldimethylsilanyloxy)hex-2-enoyl]oxazolidin-2-one. 95% NaH (2.90 g, 115 mmol) is suspended in 250 mL CH_2Cl_2 and cooled to 0 °C before adding 2-oxazolidinone (5.00 g, 57.4 mmol). After bubbling ceases, the suspension is cooled to -78 °C and propenoyl chloride is added. The reaction is warmed to room temperature over 1 h. The reaction is stirred for an additional 18 h at which point TLC analysis (2:3 EtOAc/hexanes; R_f product = 0.4) indicates the presence of product. The solution is filtered through a short pad of silica gel, rinsing with copious CH_2Cl_2 until no further product is obtained from the washes. The solvent is removed under reduced pressure without heat to yield 3-(2-propenoyl)oxazolidin-2-one as white crystals (4.30 g, 30.5 mmol, 53%). The 3-(2-propenoyl)oxazolidin-2-one product is characterized by ^{1}H NMR before the cross metathesis reaction. *tert*-Butyldimethylpent-4-enyloxysilane (554 mg, 2.76 mmol) and 3-(2-propenoyl)oxazolidin-2-one (300 mg, 2.13 mmol) are placed in a 25 mL round bottom flask and 10 mL of CH_2Cl_2 is added. The solution is heated to reflux before adding (4,5-DihydroIMES)Cl_2-Ru=CH-*o*-O-*i*PrC_6H_4 (53 mg, 0.085 mmol)[3] in 5 ml CH_2Cl_2 via cannula. The reaction is heated at reflux for 36 h before cooling and concentrating. Purification by silica gel chromatography (3:1 hexanes/EtOAc) yielded **5c** as a colorless oil (625 mg, 1.99 mmol, 94%). IR (neat): 2953 (s), 2930 (s), 2857 (s), 1781 (s), 1685 (s), 1636 (s); ^{1}H NMR (400 MHz): δ 7.27-7.15 (2H, m, C**H**=C**H**CO), 4.41 (2H, dd, *J* = 7.6, 7.6 Hz, OC**H**$_2$CH$_2$N), 4.07 (2H, dd, *J* = 8.0, 7.2 Hz, NC**H**$_2$CH$_2$), 3.64 (2H, t, *J* = 6.2 Hz, SiOC**H**$_2$), 2.39-2.32 (2H, m, CH=CHC**H**$_2$), 1.74-1.66 (2H, m, CH$_2$C**H**$_2$CH$_2$), 0.89 (9H, s, SiC(C**H**$_3$)$_3$), 0.04 (6H, s, Si(C**H**$_3$)$_2$); ^{13}C NMR (100 MHz): δ 165.4, 153.6, 151.6, 120.2, 62.4, 62.2, 42.9, 31.3, 29.4, 26.1, 18.5 (3C), -5.2 (2C); Anal Calcd for $C_{15}H_{27}NO_4Si$: C, 57.47; H, 8.68; Found C, 57.24; H, 8.46.

Representative experimental procedure for Cu-catalyzed conjugate addition of dialkyl zinc reagents to α,β-unsaturated N-Acyloxazolidinones: A 13x100 mm test tube is charged with $(CuOTf)_2$•PhH (1.3 mg, 2.5 μmol) and 4 (3.7 mg, 6.0 μmol) under an atmosphere of nitrogen in a glove box. The tube is sealed with a septum and removed from the glove box. 3-But-2-enoyloxazolidin-2-one (**5a**, 39 mg in 1.0 mL of toluene, 0.25 mmol) is added via cannula, rinsing

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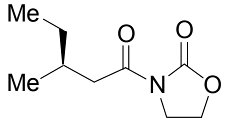
[3] (a) J. S. Kingsbury, J. P. A. Harrity, P. J. Bonitatebus, A. H. Hoveyda, *J. Am. Chem. Soc.* **1999**, *121*, 791-799; (b) S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 8168-8179; (c) J. S. Kingsbury, S. B. Garber, J. M. Giftos, B. L. Gray, M. M. Okamoto, R. A. Farrer, J. T. Fourkas, A. H. Hoveyda, *Angew. Chem.* **2001**, *113*, 4381-4386; *Angew. Chem. Int. Ed.* **2001**, *40*, 4251-4255. This catalyst is now available from Aldrich (Hoveyda-Grubbs' Catalyst).

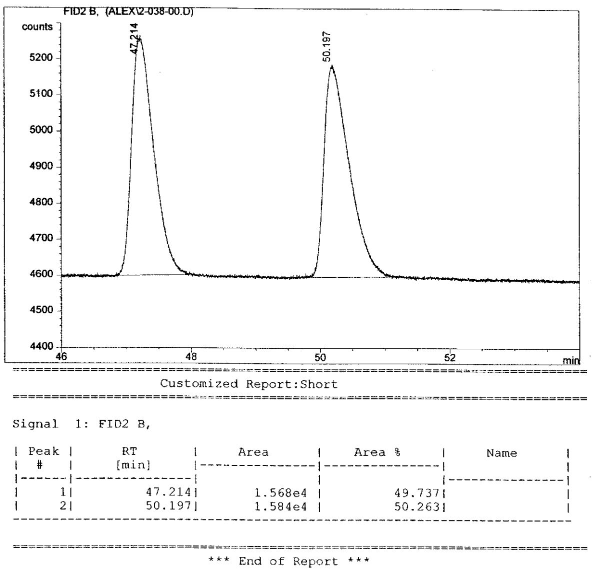
with an additional 0.7 mL of toluene. After cooling the tube to 0 °C, Et_2Zn (caution, pyrophoric, 77 μL, 0.75 mmol) is added with stirring. The mixture was stirred for 2.5 h at 0 °C before dilution with Et_2O (2 mL) followed by aqueous 1M HCl (2 mL) to quench. After removal of the organic layer, the aqueous layer is washed with EtOAc (3 x 2 mL). The combined organic extracts were concentrated under reduced pressure to yield a pale yellow oil. The oil was purified by silica gel chromatography (3:1 hexanes/EtOAc) to yield **6** as a colorless oil (34 mg, 0.18 mmol, 74 %).



6

***S*-(+)-3-(3-Methylpentanoyl)oxazolidin-2-one**. IR (neat): 2961 (m), 2927 (m), 2874 (m), 1780 (s), 1698 (m); ^{1}H NMR (400 MHz): δ 4.40 (2H, dd, *J* = 8.2, 8.0 Hz, $OC\mathbf{H}_2CH_2$), 4.02 (2H, dd, *J* = 8.0, 7.8 Hz, $NC\mathbf{H}_2CH_2$), 2.83 (2H, AB**X**, J_{AB} = 16.2, J_{AX} = 5.8, J_{BX} = 8.0 Hz, $C\mathbf{H}_2CO$), 1.98 (1H, AB**X** m, C**H**(Et)Me), 1.41 (1H, m, $C\mathbf{H}_2Me$), 1.26 (1H, m, $C\mathbf{H}_2Me$), 0.95 (3H, d, *J* = 6.8 Hz, $CH(Et)C\mathbf{H}_3$), 0.91 (3H, t, *J* = 7.4 Hz, $CH_2C\mathbf{H}_3$); ^{13}C NMR (100 MHz): δ 173.3, 153.7, 62.0, 42.7, 41.9, 31.3, 29.5, 19.4, 11.5; Anal Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 7.56; Found: C, 58.49; H, 7.88; HRMS Calcd for $C_9H_{15}NO_3$: 185.1052, Found: 185.1053; $[\alpha]_D^{20}$ +11.2° (*c* = 1.39, $CHCl_3$) for a 95% ee sample. Absolute configuration determined by hydrolysis to the carboxylic acid[4] and comparison of its optical rotation with literature values.[5] (see separate experimental for conversion to acid).

The optical purity of the conjugate addition adduct was established by chiral GLC analysis (β-dex, 130 °C, 20 psi); chromatograms are illustrated below:



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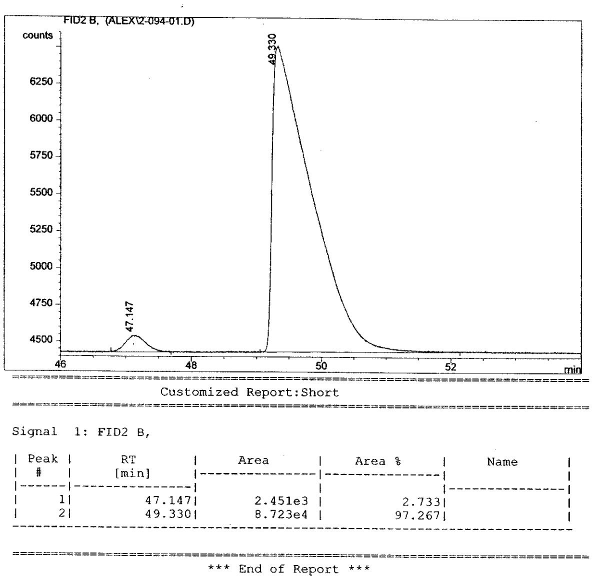

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from ACA: 95% ee

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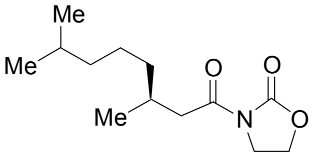
[4] D. A. Evans, T. C. Britton, J. A. Ellman, *Tetrahedron Lett.* **1987**, *28*, 6141-6144

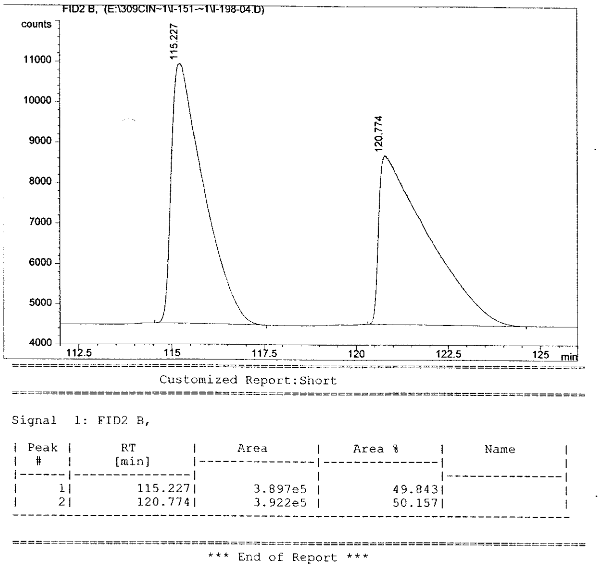
[5] A. I. Meyers, K. Kamata, *J. Am. Chem. Soc.* **1976**, *98*, 2290-2294 and references cited therein.



8

(+)-3-(3,7-Dimethyl-octanoyl)-oxazolidin-2-one. IR (neat): 2953 (m), 2920 (m), 2864 (m), 1781 (s), 1698 (s); ^{1}H NMR (400 MHz): δ 4.40 (2H, dd, *J* = 8.0, 7.6 Hz, OC**H**$_2$CH$_2$), 4.02 (2H, dd, *J* = 7.6, 7.6 Hz, NC**H**$_2$CH$_2$), 2.83 (2H, **AB**X, *J*$_{AB}$ = 16.0, *J*$_{AX}$ = 5.6, *J*$_{BX}$ = 8.0 Hz, C**H**$_2$CO), 2.04 (1H, AB**X** m, C**H**(CH$_2$R)Me), 1.52 (1H, m, C**H**Me$_2$), 1.25 (6H, m, aliphatic C**H**), 0.95 (3H, d, *J* = 6.8 Hz, C**H**$_3$), 0.86 (3H, d, *J* = 6.4 Hz, C**H**$_3$), 0.86 (3H, d, *J* = 6.4 Hz, C**H**$_3$); ^{13}C NMR (100 MHz): δ 173.2, 153.7, 62.0, 42.7, 42.3, 39.2, 37.2, 29.8, 28.1, 24.8, 22.8, 22.7, 19.9; Anal Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; Found: C, 64.47; H, 9.85; $[\alpha]_D^{20}$ +1.4° (*c* = 1.4, $CHCl_3$) for a 94% ee sample.

The optical purity of the conjugate addition adduct was established by chiral GLC analysis (β-dex, 140 °C, 25 psi); chromatograms are illustrated below:



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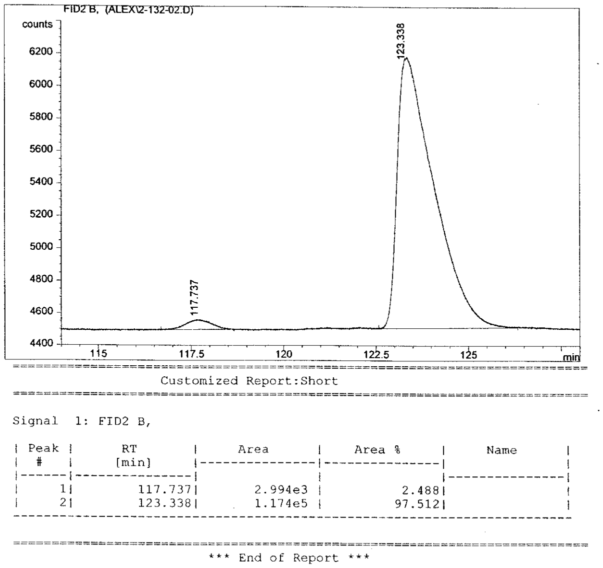
authentic racemic



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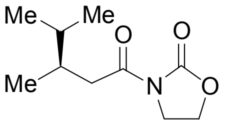
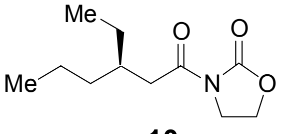
from ACA: 95% ee



9

(+)-3-(3,4-Dimethylpentanoyl)oxazolidin-2-one. IR (neat): 2962 (m), 2923 (w), 2875 (w), 1779 (s), 1697 (s), 1478 (m), 1466 (w), 1389 (s); ^{1}H NMR (400 MHz): δ 4.40 (2H, dd, *J* = 8.4, 7.6 Hz, OC**H**$_2$CH$_2$), 4.02 (1H, dd, *J* = 8.0, 7.6 Hz, NC**H**$_2$CH$_2$), 4.02 (1H, dd, *J* = 8.8, 8.0 Hz, NC**H**$_2$CH$_2$), 2.85 (2H, **AB**X, *J*$_{AB}$ = 16.0, *J*$_{AX}$ = 5.2, *J*$_{BX}$ = 8.8 Hz, C**H**$_2$CO), 1.99 (1H, m, C**H**), 1.64 (1H, m, C**H**), 0.90 (3H, d, *J* = 7.0 Hz, C**H**$_3$), 0.89 (3H, d, *J* = 7.0 Hz, C**H**$_3$), 0.87 (3H, d, *J* = 6.8 Hz, C**H**$_3$); ^{13}C NMR (100 MHz): δ 173.6, 153.6, 62.0, 42.8, 39.7, 35.2, 32.3, 20.1, 18.4, 15.8; HRMS Calcd for $C_{10}H_{17}NO_3Na$ ($M+Na^+$): 222.1106, Found: 222.1109; $[\alpha]_D^{20}$ +15.5° (*c* = 0.84, $CHCl_3$) for a 76% ee sample.

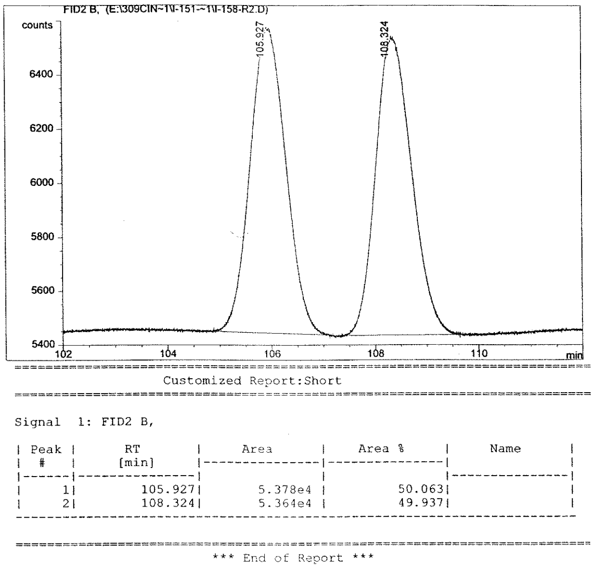
The optical purity of the conjugate addition adduct was established by chiral GLC analysis (β-dex, 125 °C, 20 psi, $t_{\mathbf{minor}}$ = 83 min, $t_{\mathbf{major}}$ = 86 min).



10

(-)-3-(3-Ethyl-hexanoyl)-oxazolidin-2-one. IR (neat): 2962 (s), 2925 (s), 2870 (s), 1785 (s), 1693 (s), 1478 (s), 1464 (s); ^{1}H NMR (400 MHz): δ 4.40 (2H, dd, *J* = 8.4, 8.0 Hz, OC**H**$_2$CH$_2$), 4.02 (2H, dd, *J* = 8.4, 7.6 Hz, NC**H**$_2$CH$_2$), 2.86 (2H, d, *J* = 6.8 Hz, C**H**$_2$CO), 1.93 (1H, m, C**H**(Et)Pr), 1.31 (6H, m, aliphatic C**H**), 0.88 (6H, m, C**H**$_3$); ^{13}C NMR (100 MHz): δ 173.6, 153.7, 62.0, 42.8, 39.3, 35.8, 35.5, 26.4, 19.9, 14.5, 10.9; Anal Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57; Found C, 61.90; H, 8.69; N, 6.72; $[\alpha]_D^{20}$ –0.6° (*c* = 1.8, CHCl$_3$) for a 94% ee sample (rotation given for conjugate addition product obtained from reaction with ligand 4).

The optical purity of the conjugate addition adduct was established by chiral GLC analysis (β-dex, 130 °C, 20 psi); chromatograms are illustrated below:



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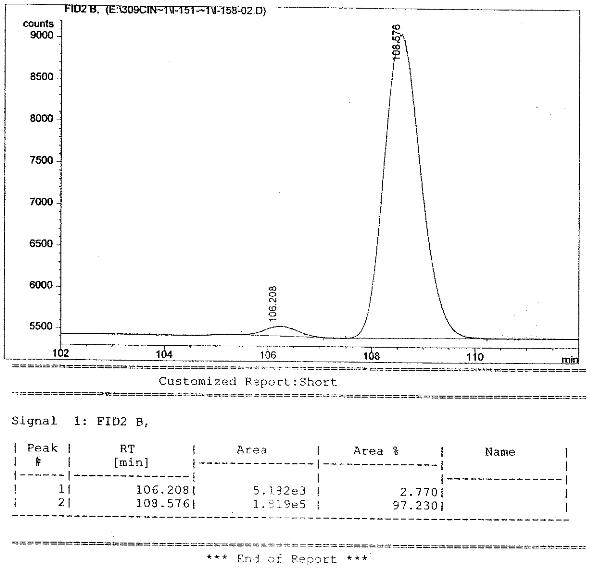
authentic racemic



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Signal  1: FID2 B,

| Peak |     RT        |     Area      |    Area %     |     Name      |
|  #   |    [min]      |---------------|---------------|               |
|------|---------------|               |               |---------------|
|     1|      106.208|      5.182e3 |         2.770|               |
|     2|      108.576|      1.819e5 |        97.230|               |
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                    *** End of Report ***
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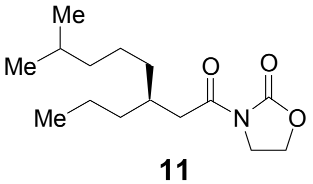
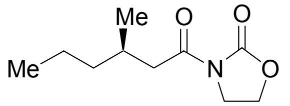
from ACA: 94% ee (D-Thr(But)-L-Val Ligand used)



11

3-(7-Methyl-3-propyl-octanoyl)-oxazolidin-2-one. IR (neat): 2955 (s), 2926 (s), 2868 (s), 1782 (s), 1700 (s), 1477 (m), 1464 (m); ^{1}H NMR (400 MHz): δ 4.40 (2H, m, OC**H**$_2$CH$_2$), 4.02 (2H, m, NC**H**$_2$CH$_2$), 2.86 (2H, **AB**qd, J_{AB} = 16.6, J_d = 6.8 Hz, C**H**$_2$CO), 1.98 (1H, m, C**H**Pr), 1.52 (1H, m, C**H**Me$_2$), 1.34-1.22 (8H, m, aliphatic C**H**), 1.18-1.10 (2H, m, aliphatic C**H**), 0.89 (3H, t, *J* = 6.8 Hz, CH$_2$C**H**$_3$), 0.86 (6H, d, *J* = 6.6 Hz, CH(C**H**$_3$)$_2$); ^{13}C NMR (100 MHz): δ 173.5, 153.7, 62.0, 42.8, 39.8, 39.4, 36.3, 34.2, 34.1, 28.1, 24.5, 22.8, 22.7, 19.9, 14.5; HRMS Calcd for $C_{15}H_{27}NO_3Na$ (M+Na$^+$): 292.1889, Found: 292.1884; $[\alpha]_D^{20}$ 0° (*c* = 1.26, CHCl$_3$) for a 94% ee sample.

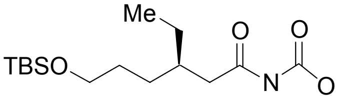
The optical purity of the conjugate addition adduct is determined by chiral HPLC analysis (Chiral Technologies Chiralpak OD, 240 nm, 99.8:0.2 hexanes/*i*-PrOH, 1.0 mLmin^{-1}, $t_{\mathbf{major}}$ = 66 min, $t_{\mathbf{minor}}$ = 62 min).



12

3-(3-Methylhexanoyl) oxazolidin-2-one. IR (neat): 2957 (s), 2925 (s), 2873 (m), 1780 (s), 1697 (s), 1480 (m), 1466 (m), 1388 (s); ^{1}H NMR (400 MHz): δ 4.40 (2H, m, OC**H**$_2$CH$_2$), 4.02 (2H, m, NC**H**$_2$CH$_2$), 2.82 (2H, **A**B**X**, J_{AB} = 16.1, J_{AX} = 5.6, J_{BX} = 8.0 Hz, C**H**$_2$CO), 2.05 (1H, ABX, m, C**H**(Me)Pr), 1.25 (4H, m, aliphatic C**H**), 0.93 (3H, d, J = 6.7 Hz, CH(**Me**)Pr), 0.88 (3H, m, CH$_2$C**H**$_3$); ^{13}C NMR (100 MHz): δ 173.2, 153.6, 62.0, 42.7, 42.2, 39.2, 29.5, 20.2, 19.8, 14.3; HRMS Calcd for $C_{10}H_{17}NO_3Na$ (M+Na$^+$): 222.1106, Found: 222.1109; $[\alpha]_D^{20}$ +3.9° (c = 0.57, CHCl$_3$) for a 96% ee sample (obtained from enantioselective reaction catalyzed by ent-**15**).

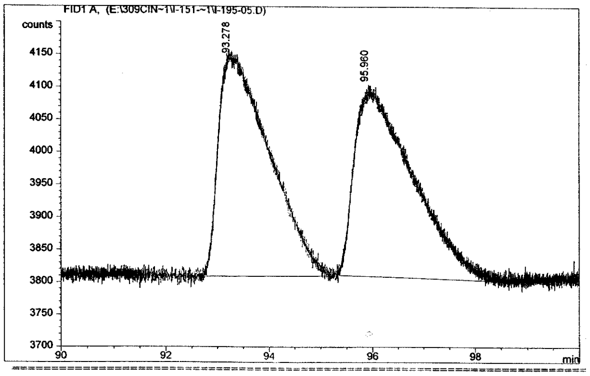
The optical purity of the conjugate addition adduct was established by chiral GLC analysis (β-dex, 125 °C, 20 psi, $t_{\mathbf{minor}}$ = 41 min, $t_{\mathbf{major}}$ = 43 min).



13

(+)-3-[6-(*tert*-Butyldimethylsilanyloxy)-3-ethylhexanoyl]oxazolidin-2-one. IR (neat): 2955 (s), 2928 (s), 2857 (s), 1785 (s), 1699 (s), 1472 (m), 1458 (m), 1385 (s); ^{1}H NMR (400 MHz): δ 4.42-4.37 (2H, m, OC**H**$_2$CH$_2$N), 4.01 (2H, dd, J = 8.4, 8.0, NC**H**$_2$CH$_2$), 3.58 (2H, t, J = 6.4 Hz, SiOC**H**$_2$), 2.87 (2H, ABqd, J_{AB} = 16.8, J_d = 6.8 Hz, C**H**$_2$CO), 1.95 (1H, m, C**H**Et), 1.60-1.25 (6H, m, aliphatic C**H**), 0.88 (9H, s, SiC(C**H**$_3$)$_3$), 0.87 (3H, t, J = 7.3 Hz, CH$_2$C**H**$_3$), 0.04 (6H, s, Si(C**H**$_3$)$_2$); ^{13}C NMR (100 MHz): δ 173.4, 153.6, 63.5, 62.0, 42.8, 39.3, 35.5, 30.0, 29.4, 26.3, 26.1, 18.5 (3C), 10.9, -5.1 (2C); Anal Calcd for $C_{17}H_{33}NO_4Si$: C, 59.44; H, 9.68; Found C, 59.70; H, 9.65; $[\alpha]_D^{20}$ +3.0° (c = 1.4, CHCl$_3$) for a >98% ee sample.

Due to insufficient separation of **13** on all available chiral GLC columns, the product is treated with 0.5 mL of 3N aqueous HCl and 0.5 mL THF for 5 min at room temperature to cleave the TBS ether (quantitative). The optical purity of this compound is determined by chiral GLC analysis (Chiraldex GTA, 110 °C, 20 psi); chromatograms are illustrated below:



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                    Customized Report:Short
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Signal  1: FID1 A,

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|  #   |     [min]      |----------------|---------------|               |
|------|----------------|                |               |---------------|
|     1|          93.278|      2.344e4   |         50.609|               |
|     2|          95.960|      2.288e4   |         49.391|               |
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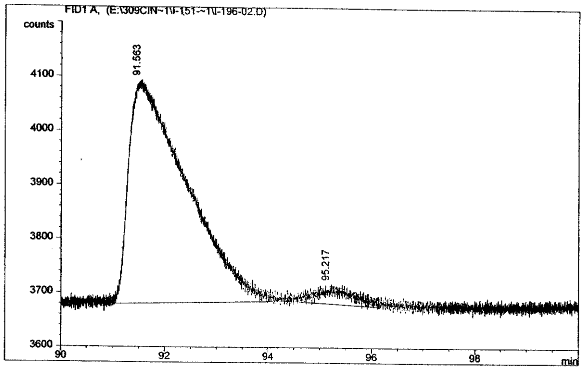
authentic racemic



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                    Customized Report:Short
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Signal  1: FID1 A,

| Peak |       RT       |     Area       |    Area %     |     Name      |
|  #   |     [min]      |----------------|---------------|               |
|------|----------------|                |               |---------------|
|     1|          91.563|      3.195e4   |         94.750|               |
|     2|          95.217|      1.770e3   |          5.250|               |
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                       *** End of Report ***
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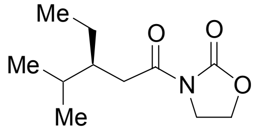
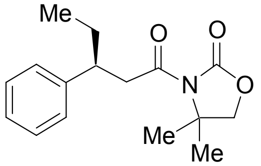
from ACA: 90% ee



14

3-(3-Ethyl-4-methylpentanoyl)oxazolidin-2-one. IR (neat): 2960 (s), 2930 (m), 2874 (m), 1780 (s), 1699 (s); ^{1}H NMR (400 MHz): δ 4.40 (2H, m, OC**H**$_2$CH$_2$N), 4.02 (2H, m, OCH$_2$C**H**$_2$N), 2.85 (2H, **AB**X, J_{AB} = 16.7, J_{AX} = 6.0, J_{BX} = 7.3 Hz, C**H**$_2$CO), 1.85 (1H, m, aliphatic C**H**), 1.75 (1H, m, aliphatic C**H**), 1.45-1.20 (2H, m, C**H**$_2$Me), 0.91-0.84 (9H, m, C**H**$_3$); ^{13}C NMR (100 MHz): δ 174.0, 153.7, 62.0, 42.9, 41.6, 36.2, 29.5, 23.7, 19.5, 18.8, 11.9; Anal Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; Found C, 61.76; H, 8.87; $[\alpha]_D^{20}$ -3.3° (*c* = 1.2, CHCl$_3$) for a 81% ee sample.

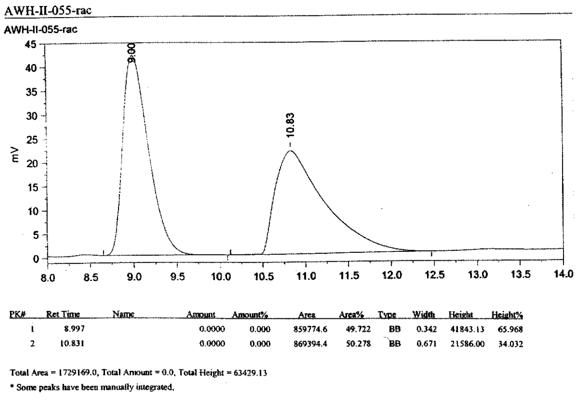
The optical purity of the conjugate addition adduct was established by chiral GLC analysis (β-dex, 125 °C, 20 psi, $t_{\mathbf{major}}$ = 155 min, $t_{\mathbf{minor}}$ = 156 min).



18

4,4-Dimethyl-3-(3-phenylpentanoyl)oxazolidin-2-one. IR (neat): 3083 (w), 3061 (w), 3027 (m), 2964 (s), 2930 (s), 2874 (m), 1775 (s), 1704 (s), 1494 (m), 1453 (s), 1393 (s), 1378 (s); ^{1}H NMR (400 MHz): δ 7.30-7.15 (5H, m, Ar**H**), 3.87 (2H, ABq, J_{AB} = 8.2 Hz, C**H**$_2$O), 3.23 (2H, **AB**X, J_{AB} = 15.6 Hz, J_{AX} = 8.8 Hz, J_{BX} = 6.2 Hz, C**H**$_2$CO), 3.07 (1H, ABX, m, C**H**CH$_2$CO), 1.78-1.58 (2H, m, C**H**$_2$Me), 1.43 (3H, s, NC(C**H**$_3$)Me), 1.31 (3H, s, NC(Me)C**H**$_3$), 0.80 (3H, t, J = 7.3 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (100 MHz): δ 173.3, 154.2, 144.0, 128.4, 127.9, 126.5, 75.2, 60.5, 44.0, 43.2, 29.7, 24.8, 24.5, 12.1; HRMS Calcd for $C_{16}H_{21}NO_3Na$ (M+Na$^+$): 298.1419, Found: 298.1424; $[\alpha]_D^{20}$ +11.5° (*c* = 1.15, CHCl$_3$) for a 86% ee sample.

The optical purity of the conjugate addition adduct was established by chiral HPLC analysis (Chiral Technologies Chiralpak OD, 254 nm, 98:2 hexanes/*i*-PrOH, 1 mL/min); chromatograms are illustrated below:

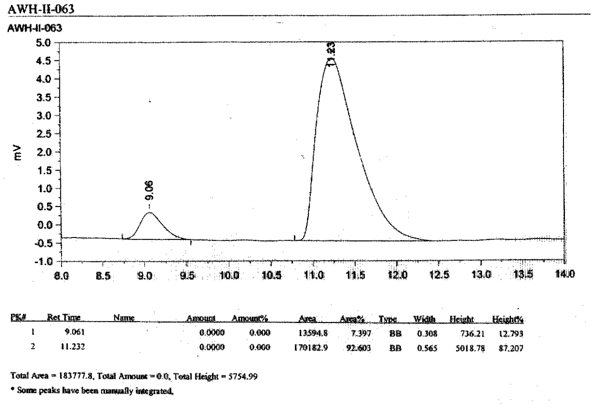


PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	8.997		0.0000	0.000	859774.6	49.722	BB	0.342	41843.13	65.968
2	10.831		0.0000	0.000	869394.4	50.278	BB	0.671	21586.00	34.032

Total Area = 1729169.0, Total Amount = 0.0, Total Height = 63429.13

* Some peaks have been manually integrated.

authentic racemic

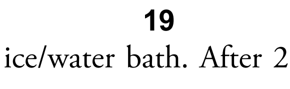


PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	9.061		0.0000	0.000	13594.8	7.397	BB	0.308	736.21	12.793
2	11.232		0.0000	0.000	170182.9	92.603	BB	0.565	5018.78	87.207

Total Area = 183777.8, Total Amount = 0.0, Total Height = 5754.99

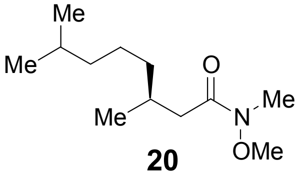
* Some peaks have been manually integrated.

from ACA: 86% ee

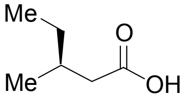


19

2,2,9-Trimethyl-5-propyldecan-3-one. 3-(3,7-Dimethyloctanoyl)oxazolidin-2-one (**8**) (48.9 mg, 0.203 mmol) is dissolved in 2 mL THF and cooled to –20 °C with stirring. *tert*-Butyllithium (1.7M / pentane, 179 μL, 0.304 mmol) is added in one portion and the reaction transferred to an ice/water bath. After 20 min, the reaction is poured in to 2 mL of 1M HCl. The aqueous layer is washed with Et_2O (3 x 7 mL), dried over $MgSO_4$ and concentrated. The crude is purified by silica gel chromatography (pipette column, 4:1 pentane/Et_2O) to yield a colorless oil (35.0 mg, 0.165 mmol, 81%). IR (neat): 2958 (s), 2926 (s), 2871 (m), 1707 (s), 1465 (m), 1365 (m); ^{1}H NMR (400 MHz): δ 2.36 (2H, **AB**X, J_{AB} = 17.2, J_{AX} = 5.9, J_{BX} = 7.6 Hz, C**H**$_2$CO), 2.04 (1H, AB**X**, m, C**H**CH$_2$CO), 1.52 (1H, m, C**H**(Me)$_2$), 1.30-1.10 (6H, m, aliphatic C**H**), 1.12 (9H, s, C(C**H**$_3$)$_3$), 0.88-0.83 (9H, m, C**H**$_3$); ^{13}C NMR (100 MHz): δ 215.8, 44.3, 44.2, 39.3, 37.3, 28.7, 28.1, 26.5, 25.0, 22.8, 22.7, 20.0 (3C); HRMS Calcd for $C_{14}H_{28}ONa$ (M+Na$^+$): 235.2040, Found 235.2038.


20

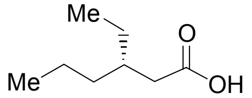
7-Methyl-3-propyloctanoic acid methoxymethyl amide. *N*,*O*-Dimethylhydroxylamine hydrochloride (104 mg, 1.07 mmol) is added to a 2-neck round bottom flask with condenser attached. 2.5 mL CH_2Cl_2 is added and the suspension cooled to 0 °C. Trimethylaluminum (2M in toluene, 536 μL, 1.07 mmol) is added and the reaction is warmed to room temperature and stirred for 30 min. 3-(3,7-Dimethyloctanoyl)oxazolidin-2-one (**8**) (51.7 mg, 0.214 mmol) in 1.5 mL CH_2Cl_2 is added via cannula, rinsing with an additional 1 mL CH_2Cl_2 and the reaction is heated at reflux for 1 h. At this point, the reaction mixture is cannulated directly into 10 mL of ice-cold 1M aqueous HCl. The organic layer is separated and the aqueous layer washed with CH_2Cl_2 (3 x 10 mL). The combined organic layers are washed with saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The residue is purified by silica gel chromatography (3:1 hexanes/EtOAc) to yield a yellow oil (34 mg, 0.16 mmol, 74%). IR (neat): 2955 (s), 2928 (s), 2870 (m), 1668 (s); ^{1}H NMR (400 MHz): δ 3.67 (3H, s, OC**H**$_3$), 3.18 (3H, s, NC**H**$_3$), 2.31 (2H, **AB**X, J_{AB} = 14.8, J_{AX} = 6.2, J_{BX} = 8.3 Hz, C**H**$_2$CO), 2.02 (1H, AB**X**, m, C**H**CH$_2$CO), 1.52 (1H, m, C**H**(Me)$_2$), 1.40-1.10 (6H, m, aliphatic C**H**), 0.93 (3H, d, J = 6.6 Hz, CHC**H**$_3$), 0.87 (3H, d, J = 6.6 Hz, CHC**H**$_3$), 0.86 (3H, d, J = 6.6 Hz, CHC**H**$_3$); ^{13}C NMR (100 MHz): δ 174.5, 61.3, 39.3, 39.2, 37.4, 29.9, 28.1, 24.9, 22.8, 22.7, 20.1; HRMS Calcd for $C_{12}H_{25}NO_2Na$ (M+Na$^+$): 238.1783, Found 238.1793.


21

***S*-(+)-3-Methylpentanoic acid.** (+)-3-(3-Methylpentanoyl)oxazolidin-2-one (**6**) (17.6 mg, 95 μmol) is dissolved in 1 mL of 1:1 THF/H_2O and cooled to 0 °C. 30 wt. % H_2O_2 in H_2O (58 μL, 571 μmol) is added, followed by LiOH⊠H_2O (8.0 mg, 190 μmol). After 30 min, peroxides are quenched with 0.42 mL of a 1.5M solution of Na_2SO_3. 2-oxazolidinone is removed from the aqueous layer by continuous extraction with CH_2Cl_2 overnight. The aqueous layer is then acidified with 1M HCl and the extraction continued for a further 12 h to obtain, after concentration under reduced pressure, the carboxylic acid as a colorless oil (11 mg, 95 μmol, >98%). IR (neat): 3000 (br), 2964 (s), 2932 (m), 2877 (m), 1710 (s), 1463 (m), 1411 (m); ^{1}H NMR (400 MHz): δ 11.5 (1H, br s, O**H**), 2.25 (2H, **AB**X, J_{AB} = 15.0 Hz, J_{AX} = 6.1 Hz, J_{BX} = 8.2 Hz, C**H**$_2$CO$_2$H), 1.88 (1H, AB**X**, m, C**H**CH$_2$CO), 1.39 (1H, m, C**H**$_2$Me), 1.24 (1H, m, C**H**$_2$Me), 0.96 (3H, d, J = 6.8 Hz, CHC**H**$_3$), 0.89 (3H, t, J = 7.4 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (100 MHz): δ 180.0, δ 41.3, δ 31.9, δ 29.4, δ 19.4, δ 11.4; Anal Calcd for

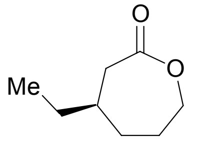
$C_6H_{12}O_2$: C, 62.04; H, 10.41; Found C, 62.14; H, 10.33; $[\alpha]_D^{20}$ +2.4° (*c* =0.81, $CHCl_3$) for a 93% ee sample.

Proof of stereochemistry: literature: [5] $[\alpha]_D^{24}$ -3.29° (neat) for a 40% ee sample of the R enantiomer.



***S*-(-)-3-Ethylhexanoic acid**. Hydrolysis procedure as above. IR (neat): 3000 (br), 2961 (s), 2930 (s), 2876 (s), 1710 (s), 1463 (s), 1409 (s); ^{1}H NMR (400 MHz): δ 11.3 (1H, br s, O**H**), 2.28 (2H, d, J = 6.8 Hz, C**H**$_2$CO$_2$H), 1.82 (1H, m, CH$_2$C**H**(Et)Pr), 1.33 (6H, m, aliphatic C**H**), 0.91 (3H, t, J = 4.8 Hz, C**H**$_3$), 0.89 (3H, t, J = 5.8 Hz, C**H**$_3$); ^{13}C NMR (100 MHz): δ 180.6, 38.7, 36.2, 35.8, 26.4, 19.8, 14.4, 10.9; Anal Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18; Found C, 66.90; H, 11.07; $[\alpha]_D^{20}$ –1.8° (*c* = 1.2, $CHCl_3$) for a 91% ee sample obtained by hydrolysis of conjugate addition product catalyzed by ent-4.

Proof of stereochemistry: literature: [5] $[\alpha]_D^{24}$ +0.57° (neat) for a 31% ee sample of the R enantiomer.

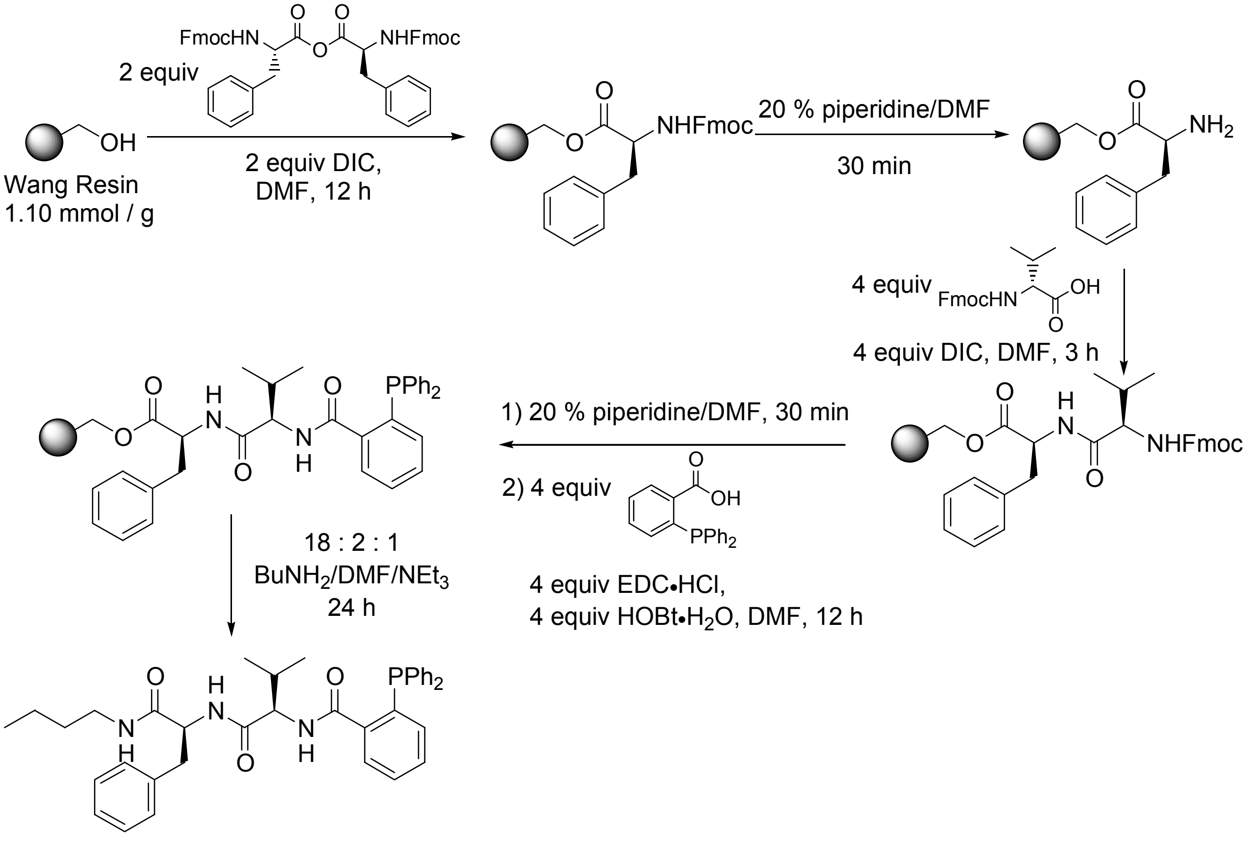


4-Ethyloxepan-2-one: 3-[6-(*tert*-Butyldimethylsilanyloxy)-3-ethylhexanoyl] oxazolidin-2-one (**13**, 104 mg, 0.303 mmol) is dissolved in 2 mL THF and 2 mL of 3M HCl is added. After 30 min, the reaction is neutralized with sat. $NaHCO_3$ and washed with Et_2O (3 x 5 mL). The combined organic layers are dried over $MgSO_4$ and purified by silica gel chromatography (1:1 Et_2O/pentane to Et_2O) to yield the deprotected conjugate addition adduct (63 mg, 0.27 mmol, 91%). 3-(6-Hydroxyhexanoyl)oxazolidin-2-one (10.9 mg, 48 μmol) is hydrolyzed as above but with the second extraction carried out for 24 h to obtain the carboxylic acid (7.7 mg, 48 μmol, >98%). The carboxylic acid (7.6 mg, 47 μmol) is diluted in 5 mL toluene and *p*TsOH (1.6 mg, 10 μmol) and activated 3 Å molecular sieves (1.9 mg) are added. The reaction is heated at reflux for 3.5 h before cooling to room temperature. The solution is diluted with 5 mL pentane and purified by silica gel chromatography (pentane to 1:1 pentane/Et_2O) to yield the desired lactone (6.4 mg, 45 μmol, 96%). IR (neat): 2962 (m), 2925 (m), 2864 (m), 1730 (s), 1286 (m); ^{1}H NMR (400 MHz): δ 4.28-4.12 (2H, m, OC**H**$_2$), 2.62 (1H, ABdd, J_{AB} = 13.6 Hz, J_{dd} = 2.0, 1.3 Hz, C**H**$_2$CO), 2.52 (1H, ABd, J_{AB} = 13.6, J_d = 9.9 Hz, C**H**$_2$CO), 2.00-1.60 (4H, m, aliphatic C**H**), 1.50-1.30 (3H, m, aliphatic C**H**), 0.92 (3H, t, J = 7.3 Hz, C**H**$_3$); ^{13}C NMR (100 MHz): δ 175.4, 69.4, 40.0, 35.8, 34.7, 29.1, 27.9, 11.4; HRMS Calcd for $C_8H_{14}O_2Na$ (M+Na$^+$): 165.0891, Found 165.0886.

Ligand Screening Data

All solid phase reactions are performed in Bio-Spin Chromatography Columns (1.2 mL capacity, from Bio-Rad, cat.# 732-6008). 100-200 mesh Wang resin (1.1 mmol/g) is purchased from NovaBiochem. Sequencing grade DMF is purchased from Fisher Scientific and purified by bubbling dry nitrogen through for 24 h. The solvent is then stored over oven dried 4 Å molecular sieves. CH_2Cl_2 is used as reagent grade, undistilled. Piperidine and all Fmoc-protected amino acids are purchased from Advanced ChemTech and used without purification. *n*-butylamine and NEt_3 are distilled from CaH_2.

Multiple ligands for screening are prepared according to the general synthetic sequence shown in Scheme 1. 1.10 mmol/g Wang resin (100 mg, 0.110 mmol) is added to a tube and swelled in 2 mL of DMF for at least 2 h. Fmoc-Phe-OH (170 mg, 0.440 mmol) is dissolved in a minimal amount of CH_2Cl_2, adding DMF if necessary to aid dissolution. DIC (35 µL, 0.22 mmol) is added and the solution is left to stand for 10 min. A stream of nitrogen is used to remove the solvent and the residue is taken up in 2 mL DMF. DMAP (0.7 mg, 5.5 µmol) is added to the anhydride. Excess DMF is removed from the pre-swelled resin by filtration and the solution of symmetrical anhydride is added to the resin. Another 2 equiv of DIC (35 µL, 0.22 mmol) are added to the vessel and it is agitated for 24 h. At this time, the solvent is removed by filtration and the resin washed with DMF (10 x 2 mL). Uncoupled free amine sites are blocked by agitating the resin in a solution of acetic anhydride (42 µL, 0.44 mmol) in 2 mL DMF. If desired, resin loading can be calculated by standard methods.[6] Typical loadings are in the range 0.88 mmol to 1.10 mmol (80% to quantitative).



Scheme 1

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[6] A useful reference for solid phase synthesis protocols was found in the technical section of the Novabiochem catalogue. Method for determining resin loading is as follows: 1. Take 3 x 10 mm matched UV cells. 2. Weigh dry Fmoc amino acid resin (approximately 1 µmol with respect to Fmoc) into cells 2 and 3. Dispense freshly prepared 20% piperidine in DMF (3 mL) into each of the three UV cells. 3. Agitate the resin mixture with the aid of a Pasteur pipette for 2-3 minutes (take care not to cross contaminate). 4. Place the cells in a spectrophotometer using cell 1 as the reference (background). Take the reading of absorption for cells 2 and 3 and estimate the resin attachment by the following equation: Fmoc loading (mmol/g) = $(\text{Abs}_{\text{sample}} - \text{Abs}_{\text{reference}})/(1.65 \times \text{mg of resin})$.

Deprotection is achieved by agitating the resin in a 20% piperidine/DMF solution for 30 min. This is promptly followed by washing 10 times with 2 mL DMF. Fmoc-D-Val-OH (149 mg, 0.440 mmol) is added to the washed resin, followed by 2 mL DMF and DIC (69 µL, 0.44 mmol). The reaction vessel is agitated for 2-3 h before washing the resin 10 times with 2 mL DMF. The deprotection and washing sequence is repeated. 2-(Diphenylphosphino)benzoic acid (135 mg, 0.440 mmol), EDC•HCl (84 mg, 0.44 mmol) and HOBt•H_2O (67 mg, 0.44 mmol) are dissolved in 2 mL DMF and added to the resin and the vessel agitated for 12 h. After washing 10 times with 2 mL DMF, 2 mL of an 18:2:1 solution of *n*-butyl amine:DMF:NEt_3 is added to the resin and the vessel is once again agitated for 12 h. The solution is drained off in to a test tube and the resin rinsed 3 times each with 2 mL DMF, 2 mL toluene and 2 mL MeOH. The combined organic washes are concentrated under reduced pressure and the residue purified by silica gel chromatography (1:1 hexanes/EtOAc). On this scale, a simple jumbo pipette column (8 mm x 75 mm) was adequate to achieve pure products by ^{1}H NMR. Typical yields from 100 mg resin are 4 mg to 28 mg (7 to 45%). Synthesis of ligands with branched AA2 residues (for example Val, Tle, Thr) often failed. This could be due either to failed coupling of the first amino acid residue under the above conditions or to failed cleavage from the resin.

Ligand Screening Results

Ligand screening is carried out for the conversion of **5a** to **6**. Reactions are run for 24 h at 4 °C. All reactions proceeded to >98% conversion.

AA1 screening is carried out first with AA2 = L-Phe. The results are presented below in Chart 1. D-Val is usually included in the AA1 ligand screen to check that L, D ligands (as opposed to the usual L, L ligands) are not more selective ligands for the reaction. However, in this case, as can be seen from the data, D-Val, L-Phe provides superior enantioselectivity to the L-Val, L-Phe ligand. Within peptide catalyzed reactions studied in these laboratories, this is the first example of a D,L ligand providing higher selectivity. From this, result, it was decided that D, L ligands should also be screened. The more cost effective way to do this is not to purchase all the D amino acids for AA1 but simply to switch AA2 from L-Phe to D-Phe and repeat the screen. The combined results for both AA1 screens are shown in Chart 2. The best ligand found from the AA1 screen is that with AA1 = L-Thr(But) and AA2 = D-Phe. Therefore, AA1 was set to D-Thr(But) and AA2 was screened (D-Thr(But) was chosen as AA1 instead of L-Thr(But) so that L-AA2s could be used in the screen).

The data for the AA2 screen are shown in Chart 3 (blank entries represent failed ligand synthesis from solid support, not 0% ee; ligands with AA2 = Val, Thr(But) and Tle also failed on solid support and were instead synthesized by standard solution phase methods). AA2 = Val provides the highest enantioselectivity for the conjugate addition at 95% ee. There are also several other promising ligand candidates but Val was chosen as AA2 due to its superior selectivity as well as the relatively low cost of the unnatural D-antipode (cost of Boc-D-Val-OH from Advanced ChemTech is $115 / 25 g, whereas Boc-L-Val-OH costs $35 / 25 g).

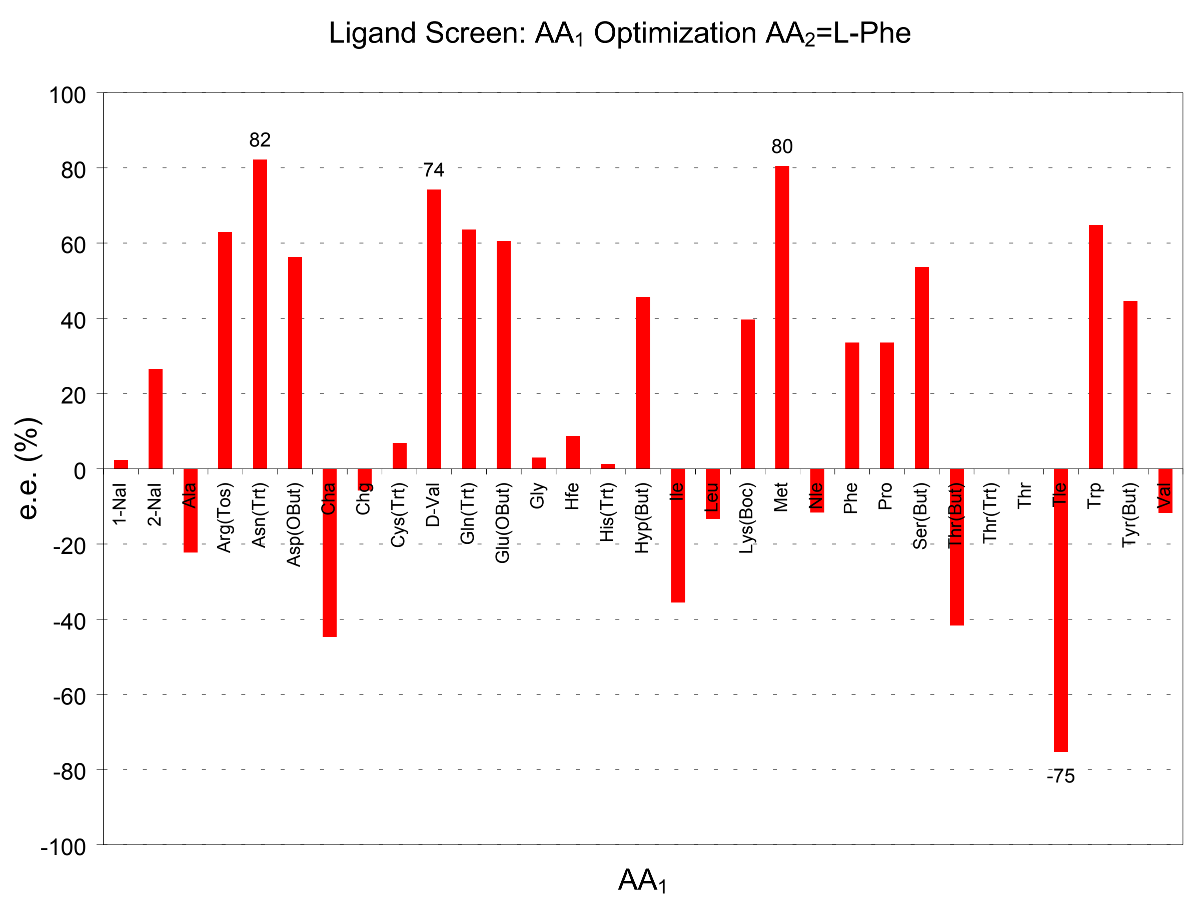
Ligand Screen: AA$_1$ Optimization AA$_2$=L-Phe
100
80
60
40
20
0
-20
-40
-60
-80
-100
e.e. (%)
82
74
80
-75
1-Nal
2-Nal
Ala
Arg(Tos)
Asn(Trt)
Asp(OBut)
Cha
Chg
Cys(Trt)
D-Val
Gln(Trt)
Glu(OBut)
Gly
Hfe
His(Trt)
Hyp(But)
Ile
Leu
Lys(Boc)
Met
Nle
Phe
Pro
Ser(But)
Thr(But)
Thr(Trt)
Thr
Tle
Trp
Tyr(But)
Val
AA$_1$

Chart 1

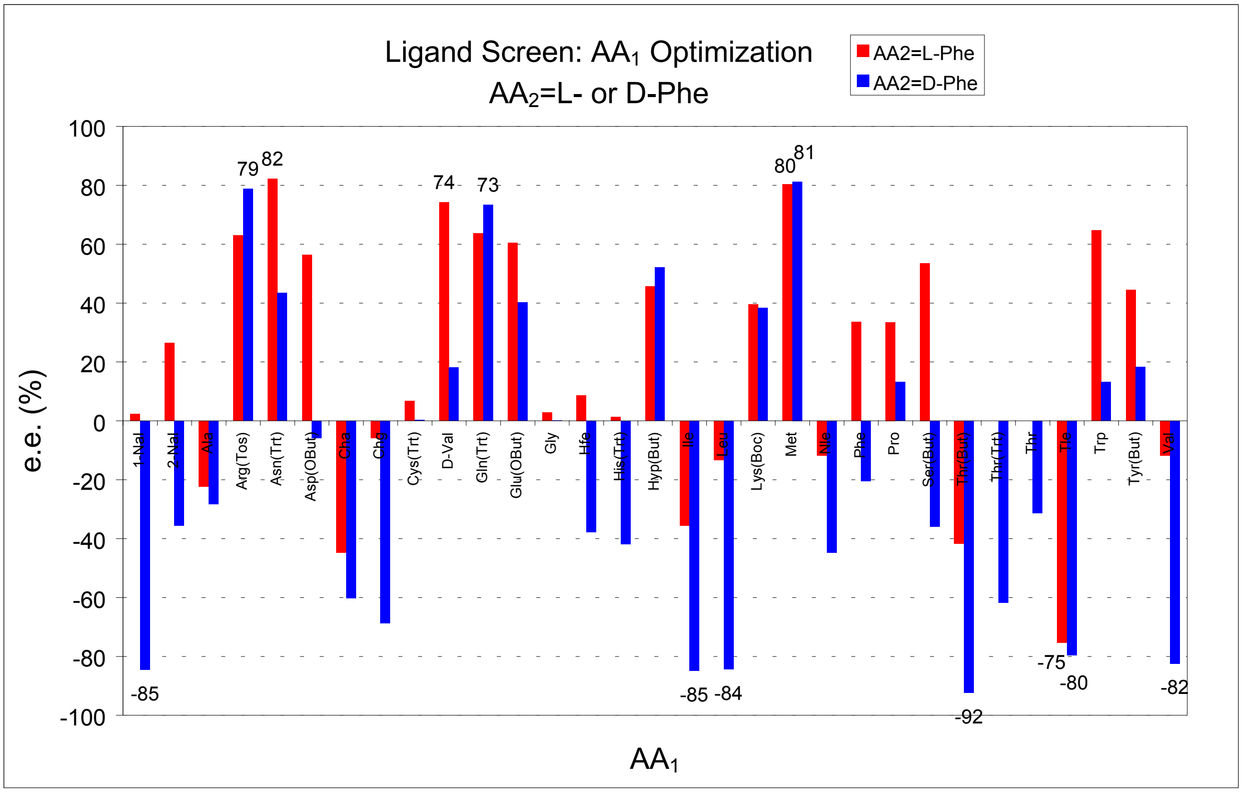

Chart 2

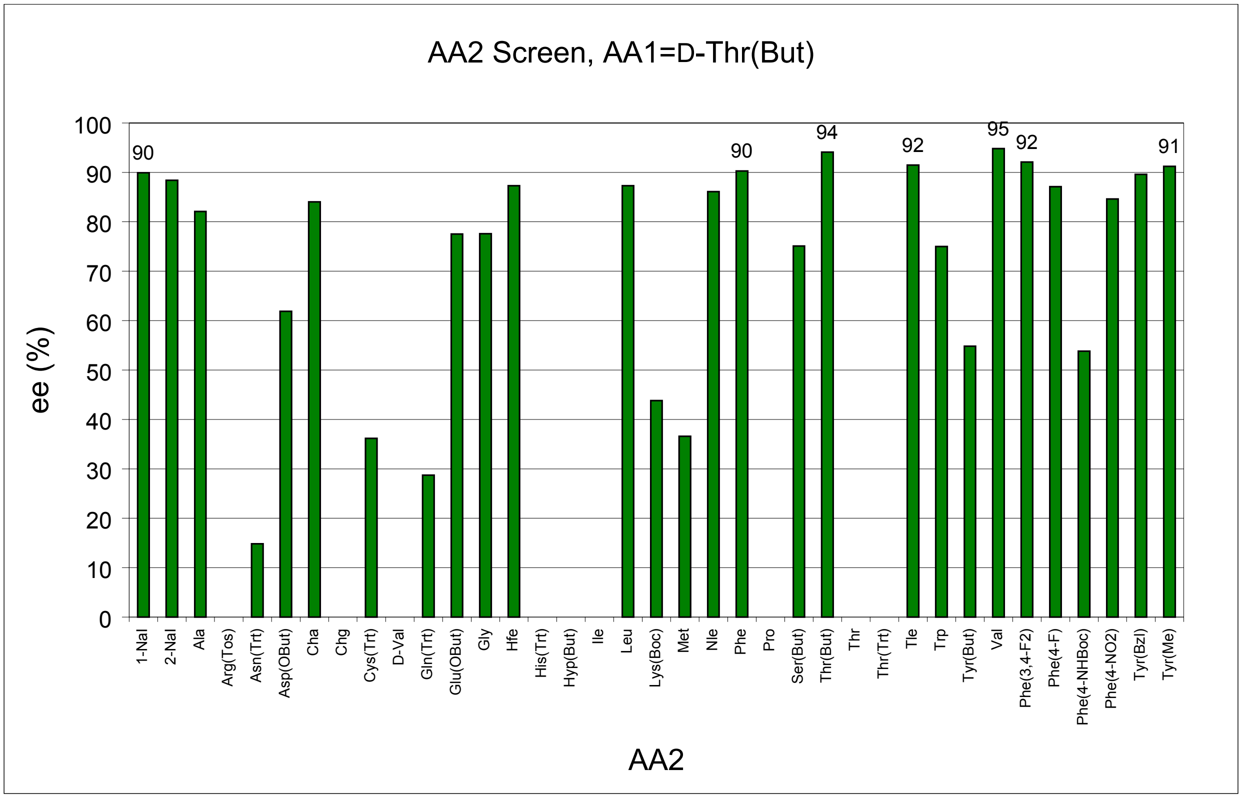

Chart 3