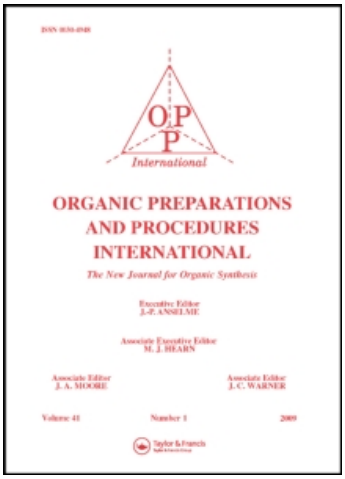

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Recent Advances in Stereoselective Synthesis and Application of β-Amino Acids

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Recent Advances in Stereoselective Synthesis and Application of β-Amino Acids

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Introduction

β-Amino acids might be regarded as the building blocks that nature overlooked. Although seldom used in nature, scientists have recognized the importance of β-amino acids in the design of many molecules. The structure of the β-amino acid allows the residue to be used as a scaffold on which to affix different functionalities. The attached functional groups frequently govern the conformational arrangement the residue adopts. It is this unique anatomy of the β-amino acid that has seen its widespread use as a tool in the design and application of many structural classes.

Given β-amino acids have found extensive applicability in many areas, a plethora of synthetic procedures to access these residues have been published. Such is the range of the literature on β-amino acid synthesis, a number of reviews[1–31] have been published; the most recent by Juaristi.[1] The aim of this review is to provide an update on advances in the stereoselective synthesis of β-amino acids during the period of 2007 to early 2009. The review will also cover recent advances in applications of β-amino residues. The application of β-residues will be divided on the basis of the β-amino acid structural class.

In the past decade, increasing work has been devoted to the study of β-amino acids. This is because they are recognized not only as pharmacologically important compounds but also are able to adopt stable and well-organised conformations. β-Peptides are stable to proteolytic degradation in vitro and in vivo, an important advantage over natural peptides and proteins.[32,33]

The β-amino residues mentioned herein will be identified, according to the nomenclature suggested by Seebach (*Figure 1*).[11]

The typical procedures reported are reproduced from the references given.

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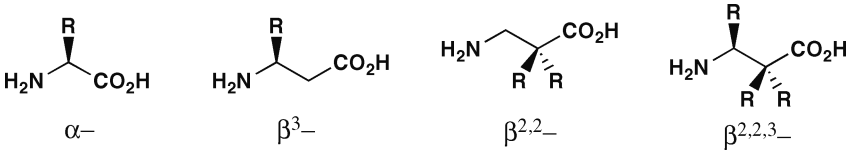
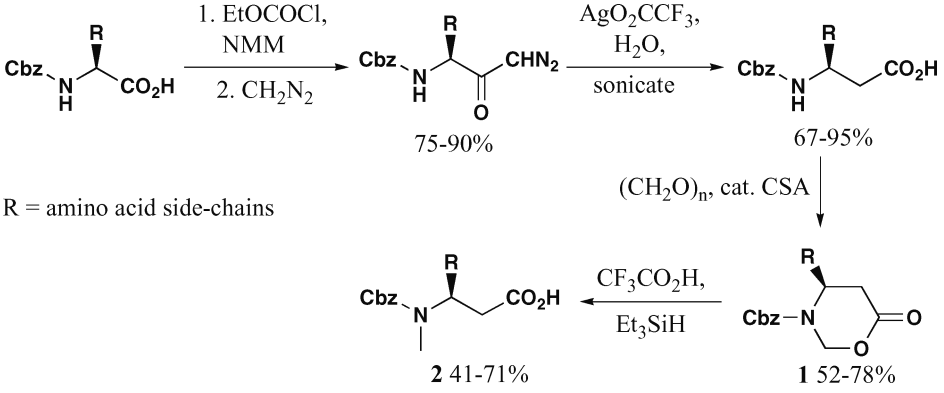


Figure 1

I. β-Amino Acids by α-Amino Acid Homologation

The Arndt-Eistert homologation is one of the most highly utilized routes to access β^3-amino acids. Such is its popularity there has been a multitude of variations and adaptations that continue to populate the literature.[1,8,16,25,29–31]

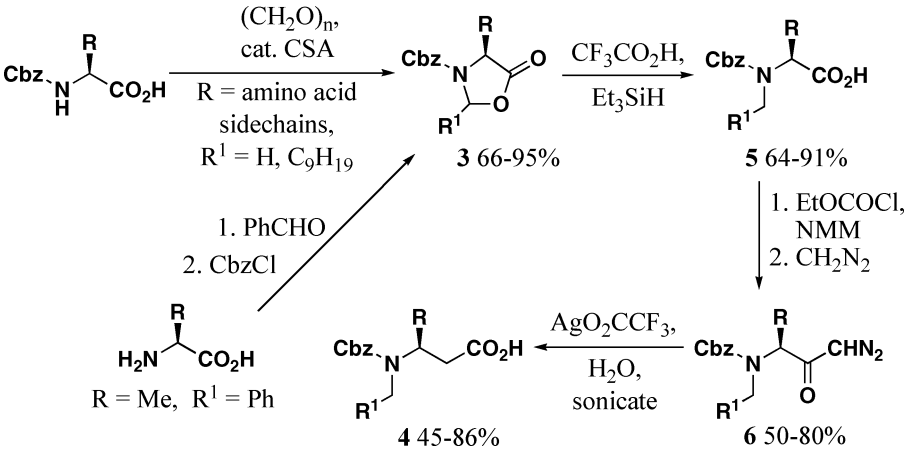
The Arndt-Eistert transformation was recently used in conjunction with 1,3-oxazolidin-5-ones and 1,3-oxazinan-6-ones **1** to produce twenty *N*-methyl-β^3-amino acids **2**.[32,33] The research found that synthesis of the *N*-methyl-β^3-residues utilizing 1,3-oxazinan-6-ones **1**, proceeds in lower than expected yields (*Scheme 1*). However, the use of 1,3-oxazolidin-5-ones **3** allows for smooth conversion of the twenty common α-amino acids to their *N*-methyl homologues using various protective group strategies (*Scheme 2*).[34,35] In an adaptation of this process, Govender and Arvidsson were able to improve the efficiency of the process using microwave technology.[36] This methodology was extended utilizing 1,3-oxazolidin-5-ones **3** in the synthesis of some *N*-alkyl-β^3-amino acids **4** (*Scheme 2*).[37]



Scheme 1

(4S)-Benzyloxycarbonyl-4-(1-methylethyl)-6-oxo-1,3-oxazinane (1). Typical Procedure.[34]

To N-benzyloxycarbonyl β^3-valine (265 mg, 1 mmol) in dry $PhCH_3$ (30 mL) was added CSA (23 mg, 0.1 mmol), paraformaldehyde (180 mg, 6 mmol) and activated 4Å molecular sieves (150 mg) under an inert atmosphere. The reaction mixture was stirred at 90°C for 2–4 h. The reaction was monitored by TLC. The mixture was allowed to cool and filtered through Celite®. The filtrate was diluted with EtOAc (30 mL) and the organic layer was washed with saturated $NaHCO_3$ (20 mL) and H_2O (20 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo. The residue was purified using column



Scheme 2

chromatography eluting with 20–45% EtOAc-hexane to afford the (4S)-benzyloxycarbonyl-4-(1-methylethyl)-6-oxo-1,3-oxazinane ***1*** *as a clear colourless oil (180 mg, 65% yield). Found: M^+, 277.1309; $C_{15}H_{19}NO_4$ requires M^+, 277.3157. $[\alpha]_D^{20}$ +147.8 (c, 1.0 in MeOH). ν_{max}(NaCl)/cm^{-1} 2964, 2800 (CH), 1761, 1714 (CO), 1455, 1262, 1155, 1130, 1009, 990, 772, 738, 698. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (5H, s, ArH), 5.89 (1H, bs, H-2A), 5.16 (2H, s, $ArCH_2$), 4.89 (1H, d, J 10.8 Hz, H-2B), 4.12–4.05 (1H, m, H-4), 2.72 (1H, dd, J 7.0 and 16.1 Hz, H-5A), 2.54 (1H, dd, J 10.5 and 16.1 Hz, H-5B), 2.10–1.99 (1H, m, NCHC**H**), 0.92–0.88 (6H, m, CH(C**H**$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 154.7 (CO), 135.1 (Aryl C), 128.3, 128.3, 127.8 (Aryl CH), 72.8 (C-2), 67.9 ($ArCH_2$), 54.5 (C-4), 31.7 (NCH**C**H), 31.3 (C-5), 18.2 (CH_3**C**CH_3), 16.3 (**C**H_3CCH_3).*

(3S)-N-Benzyloxycarbonyl-3-aminomethyl-4-methylpentanoic Acid tert-Butylammonium Salt (2). Typical Procedure.[34,35]

*(4S)-Benzyloxycarbonyl-4-(1-methyl-ethyl)-6-oxo-1,3-oxazinane (***1***, 277 mg, 1 mmol) was dissolved in CH_2Cl_2 (min. vol.) and CF_3CO_2H (50:50, v:v). Et_3SiH (349 mg, 3 mmol) was added and the solution was stirred for 48 h. $PhCH_3$ (15 mL) was added to the solution and it was then evaporated in vacuo, and this process was repeated 3 times to remove any trace of CF_3CO_2H. The residue was taken up in Et_2O (30 mL) and extracted with saturated $NaHCO_3$ (20 mL × 3). The aqueous layer was adjusted to pH 2 with dilute HCl solution, and extracted with EtOAc (25 mL × 3). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The free acid was taken up in anhydrous Et_2O (min. vol.) and treated with t-$BuNH_2$ (110 mg, 1.05 mmol). A precipitate slowly forms. The addition of hexane, dropwise, can aid the precipitation process. Stirring was generally continued for 16 h. The solid was filtered off and washed with a cold Et_2O/hexane solution to obtain the (3S)-N-benzyloxycarbonyl-3-aminomethyl-4-methylpentanoic acid tert-butylammonium salt* ***2*** *as a white solid (222 mg, 63% yield). Found: M-H, 278.1396; $C_{15}H_{20}NO_4$ requires M-H, 278.1392. Mp 99–101°C. $[\alpha]_D^{21}$ −7.5 (c, 1.1 in MeOH). ν_{max}(KBr)/cm^{-1} 3408 (OH), 2937, 2928, 2742, 2635 (CH), 2361, 2341, 2224 (H_3N^+), 1689, 1638 (CO), 1543, 1406, 1324, 969, 700, 672. ^{1}H NMR (300 MHz, D_2O) (rotamers) δ 7.29–7.21 (5H, m, ArH), 5.04–4.89*

*(2H, m, $ArCH_2$), 3.93–3.83 (1H, m, NCH), 2.65–2.59 (3H, m, NCH_3), 2.44–2.10 (2H, m, CH_2CO), 1.65–1.57 (1H, m, NCHC**H**), 1.20 (9H, s, $(CH_3)_3$), 0.76–0.60 (6H, m, $(CH_3)_2$). ^{13}C NMR (75 MHz, D_2O) (rotamers) δ 180.2, 180.1, 158.2, 157.7 (CO), 136.5, 136.3 (Aryl C), 128.4, 128.3, 127.9, 127.5, 127.2 (Aryl CH), 67.2, 66.9 ($ArCH_2$), 60.6 (NCH), 51.6 (**C**$(CH_3)_3$), 38.8, 38.7 (**C**H_2CO), 29.9 (NCH_3), 28.5 (NCH**C**H), 26.3 (C(**C**$H_3)_3$), 18.7, 18.6, 18.5 ($(CH_3)_2$).*

(3S)-N-Benzyloxycarbonyl-3-aminomethyl-1-diazo-5-methyl-hexan-2-one (6). Typical Procedure.[34]

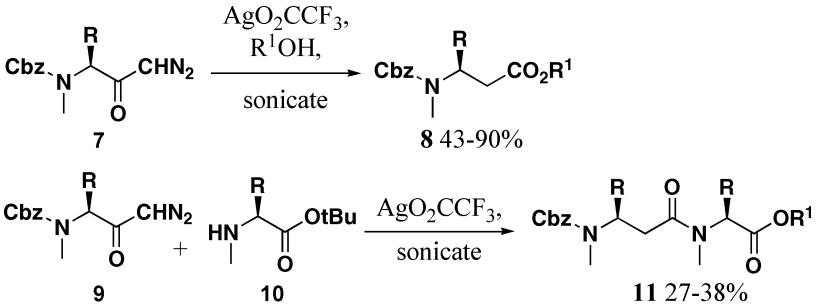
*N-Benzyloxycarbonyl-N-methyl leucine (**5**, 279 mg, 1 mmol) was dissolved in anhydrous THF (5 ml/mmol) and the solution was cooled to –15°C. To the solution, EtOCOCl (114 mg, 1.05 mmol) and N-methylmorpholine (106 mg, 1.05 mmol) were added successively and the mixture was stirred for 15 min before an anhydrous CH_2Cl_2 solution of CH_2N_2 (5 mmol) (CAUTION!) was added slowly to the mixture. The yellow solution was allowed to warm to room temperature and it was stirred for 1 h. Excess CH_2N_2 was destroyed by addition of AcOH. The mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (30 mL). The organic phase was washed successively with saturated $NaHCO_3$ (25 mL), 10% citric acid solution (25 mL) and brine (25 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was subjected to silica column chromatography, eluting with 25–45% EtOAc-hexane to yield (3S)-N-benzyloxycarbonyl-3-aminomethyl-1-diazo-5-methyl-hexan-2-one **6** as a clear yellow oil (164 mg, 54% yield). Found: M^+H, 304.1664; $C_{16}H_{22}N_3O_3$ requires M^+H, 304.1661. $[\alpha]_D^{18}$ −97.8 (c, 0.13 in CH_2Cl_2). ν_{max}(NaCl)/cm^{-1} 2957, 2871 (CH), 2106 (CHN_2), 1669, 1646 (CO), 1468, 1347, 1310, 1163, 1131, 771, 753, 736, 698. ^1H NMR (300 MHz, $CDCl_3$) δ 7.21–7.12 (5H, m, ArH), 5.30–5.18 (1H, m, CHN_2), 5.03 (2H, s, $ArCH_2$), 4.70–4.49 (1H, m, NCH), 2.67 (3H, s, NCH_3), 1.54–1.49 (2H, m, NCHC**H**$_2$), 1.38–1.34 (1H, m, CH_2C**H**), 0.81–0.68 (6H, m, $(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 192.5, 156.8, 155.9 (CO), 136.1, 135.8 (Aryl C), 128.0, 127.7, 127.6, 127.2 (Aryl CH), 67.0 ($ArCH_2$), 60.1, 60.0 (CHN_2), 53.3 (NCH), 35.9, 35.5 (**C**H_2CH_3), 30.2, 29.2 (NCH_3), 24.2, 24.0 (CH**C**H), 22.7 (CH_3), 21.2, 20.9 (CH_3).*

(3S)-N-Benzyloxycarbonyl-3-aminomethyl-5-methylhexanoic Acid tert-Butylammonium Salt (4). Typical Procedure.[34,35]

*(3S)-N-Benzyloxycarbonyl-3-aminomethyl-1-diazo-5-methyl-hexan-2-one (**6**, 303 mg, 1 mmol) was dissolved in a solution of dioxane-water (9:1, v/v, 15 mL). On addition of CF_3CO_2Ag (2.2 mg, 0.01 mmol) the mixture was sonicated in an ultrasound bath for 30 min or until no presence of the diazoketone remained as indicated by TLC. The mixture was concentrated in vacuo. The residue was dissolved in Et_2O (20 mL) and it was washed with 10% citric acid solution (20 mL). The ethereal layer was extracted with saturated $NaHCO_3$ (25 mL × 3). The combined aqueous layers were acidified, with dilute HCl, and extracted with EtOAc (25 mL × 3). The organic extract was dried ($MgSO_4$) and evaporated in vacuo. The residue was dissolved in anhydrous Et_2O (minimal volume) and treated with t-$BuNH_2$ (77 mg, 1.05 mmol). A precipitate slowly forms. The addition of*

hexane, can aid the precipitation process. The solid was filtered off at the pump and the cake was washed with a cold Et_2O-hexane solution to obtain (3S)-N-benzyloxycarbonyl-3-aminomethyl-5-methylhexanoic acid tert-butylammonium salt ***4*** *as a white solid (264 mg, 72% yield). Found: C, 65.51; H, 9.29; N, 7.71; $C_{20}H_{34}N_2O_4$ requires C, 65.54; H, 9.35; N, 7.64%). Mp 97–101°C. $[\alpha]_D^{18}$ +7.5 (c, 1.1 in MeOH). ν_{max}(KBr)/cm^{-1} 2927 (CH), 2628, 2549, 2227 (H_3N^+), 1690, 1638 (CO), 1539, 1408, 1321, 1218, 1118, 963, 753, 698. ^{1}H NMR (300 MHz, $CDCl_3$) (rotamers) δ 7.30–7.26 (5H, m, ArH), 7.03 (3H, s, H_3N^+), 5.13–5.04 (2H, m, $ArCH_2$), 4.57 (1H, bs, NCH), 2.76 (3H, s, NCH_3), 2.39–2.21 (2H, m, CH_2CO), 1.46–1.44 (2H, m, $CHCH_2$), 1.34–1.16 (1H, m, CH_2CH), 1.26 (9H, s, $(CH_3)_3$), 0.87–0.85 (6H, m, $(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$) (318 K) δ 176.5, 156.1 (CO), 136.7 (Aryl C), 127.9, 127.3, 127.1 (Aryl CH), 66.4 ($ArCH_2$), 51.9 (NCH), 50.0 ($C(CH_3)_3$), 41.6 (CH_2CO), 41.1 (NCH_2), 28.0 (NCH_3), 24.6 (CH_2CH), 22.9 ($C(CH_3)_3$), 21.5 ($(CH_3)_2$).*

In another study, the ketene intermediate, formed in the Wolff rearrangement, was intercepted with a range of useful nucleophiles to form amides and esters. From this methodology a novel *N*-methylamino acid coupling scheme was devised (*Scheme 3*).[38]



Scheme 3

(3S)-Benzyl-N-benzyloxycarbonyl-3-aminomethyl-4-methylpentanoate (8). Typical Procedure.[38]

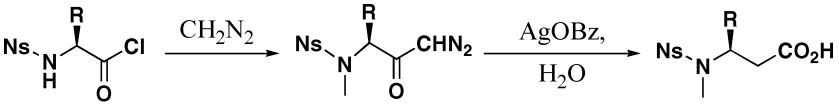
*To (3S)-N-benzyloxycarbonyl-3-aminomethyl-1-diazo-4-methylpentan-3-one (****7****, 260 mg, 0.9 mmol) dissolved in dry dioxane (5 mL) was added benzyl alcohol (3.2 mmol) and CF_3CO_2Ag (20 mg, 0.09 mmol). The solution was then sonicated for 30 min. The mixture was concentrated in vacuo and the residue was diluted with Et_2O (20 mL) and the ethereal layer was washed successively with 10% citric acid (20 mL), saturated $NaHCO_3$ (20 mL) and brine (20 mL). The ethereal layer was dried ($MgSO_4$) and concentrated under reduced pressure. The resulting oil was purified using column chromatography, eluting with 20% EtOAc-hexane, to furnish (3S)-benzyl-N-benzyloxycarbonyl-3-aminomethyl-4-methylpentanoate* ***8*** *as a clear colourless oil (44% yield). Found: M^+, 370.2027; $C_{22}H_{28}NO_4$ requires M^+, 370.2018. $[\alpha]_D^{22}$ −4.40 (c, 1.2 in CH_2Cl_2). ν_{max}(KBr)/cm^{-1} 3030, 2964 (CH), 1737, 1698 (CO), 1470, 1305, 1173, 1141, 990, 751, 697. ^{1}H NMR (300 MHz, $CDCl_3$) (rotamers) δ 7.31 (5H, s, ArH), 5.18–4.93 (4H, m, 2 x $ArCH_2$), 4.21–4.09 (1H, m, NCH), 2.78–2.47 (5H, m, NCH_3 and CH_2CO), 1.82–1.77 (1H, m, $NCHCH$), 0.94–0.81 (6H,*

*m, $(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 171.19, 170.96, 156.23, 156.04 (CO), 136.84, 136.61, 135.59, 135.45 (Aryl C), 128.29, 128.20, 128.13, 127.89, 127.59, 127.55, 127.34 (Aryl CH), 66.53, 66.21, 66.16 ($ArCH_2$), 60.06, 59.42 (NCH), 36.15, 35.69 ($\mathbf{C}H_2CO$), 30.53, 30.12, 29.88 (NCH_3), 29.40 (NCH**C**H), 19.67, 19.33 (($CH_3)_2$).*[38]

(2S)-tert-Butyl-2-((3S)-N-benzyloxycarbonyl-3-aminomethyl-butanamido)-2-methyl-amino-3-butanoate (11). Typical Procedure.[38]

*To N-benzyloxycarbonyl-3-aminomethyl-1-diazo-propan-2-one (**9**, 222 mg, 0.9 mmol) and N-methyl-α-valine tert-butyl ester tosylate salt (**10**, 1.29 g, 3.6 mmol) dissolved in dry dioxane (5 mL), was added Et_3N (3.8 mmol) and CF_3CO_2Ag (9.7 mg, 0.09 mmol). The solution was then sonicated for 45 min. The mixture was concentrated in vacuo and the residue was diluted with Et_2O (20 mL) and the ethereal layer was washed successively with 10% citric acid (20 mL), saturated $NaHCO_3$ (20 mL) and brine (20 mL). The ethereal layer was dried ($MgSO_4$) and concentrated under reduced pressure. The resulting oil was purified using column chromatography, eluting with 20% EtOAc-hexane, to furnish (2S)-tert-butyl-2-((3S)-N-benzyloxycarbonyl-3-aminomethyl-butanamido)-2-methylamino-3-butanoate **11** as a clear colourless oil (102 mg, 27% yield). Found: C, 65.60; H, 8.57; N, 6.71; $C_{23}H_{36}N_2O_5$ requires C, 65.69; H, 8.63; N, 6.66%. $[\alpha]_D^{22}$ −76.86 (c, 1.1 in CH_2Cl_2). ν_{max}(KBr)/cm^{-1} 2968, 2935 (CH), 1729, 1699, 1652 (CO), 1473, 1456, 1419, 1401, 1153, 698. ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (5H, s, ArH), 5.07 (2H, s, $ArCH_2$), 4.77–4.44 (2H, m, 2 x NCH), 2.96–2.81 (6H, m, 2 x NCH_3), 2.60–2.48 (2H, m, CH_2CO), 2.11–2.00 (1H, m, NCHC**H**), 1.41–1.39 (9H, m, $(CH_3)_3$), 1.21 (3H, s, NCHC**H**$_3$), 0.96 (3H, d, J 6.5 Hz CHC**H**$_3$), 0.78 (3H, d, J 6.7 Hz, CHC**H**$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) (323K) δ 170.94, 170.07, 168.98, 155.72 (CO), 136.89 (Aryl C), 128.29, 127.68 (Aryl CH), 81.81, 81.06 ($\mathbf{C}(CH_3)_3$), 66.85 ($ArCH_2$), 62.26 (N**C**HCH$_3$), 50.01 (NCH), 38.41, 37.81 ($\mathbf{C}H_2CO$), 31.41 (NCH_3), 30.47 (NCH_3), 27.9 ($C(\mathbf{C}H_3)_3$), 27.32 (N**C**HCH), 19.67, 19.37, 18.88, 18.46 ($CH(\mathbf{C}H_3)_2$), 17.68 (NCH**C**H$_3$).*[38]

In an improvement to the *N*-methylation process, Belsito et al. transformed N-nosyl-α-amino acid chlorides 12 to the corresponding *N*-methylated β^3-amino acids 13 in a two-step process (*Scheme 4*).[39]



12 **13** 69-81% **14** 65-83%

R = amino acid side chains

Scheme 4

Synthesis of N-Methyl-N-nosyl-(R)-aminoacyldiazomethanes (13). General Procedure.[39]

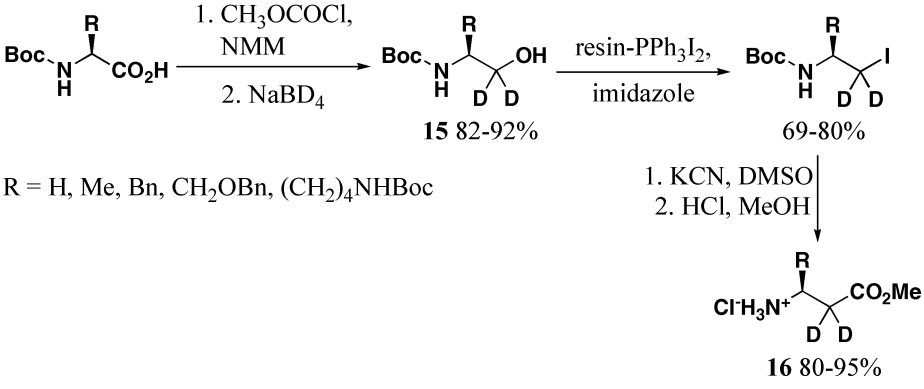
*A solution of the appropriate N-nosyl-(R)-aminoacyl chloride **12** (1 mmol) in dry CH_2Cl_2 was added dropwise to a stirred 0.66 M CH_2Cl_2 solution of CH_2N_2 (10 mmol) at 0°C. The mixture was maintained under stirring for about 50–60 min, until thin-layer chromatographic (TLC) analysis ($CHCl_3/Et_2O$ 90:10 v/v) of the reaction mixture showed complete*

conversion of the precursor into the corresponding N-methyldiazoketone ***13****. The organic solvent was removed under vacuum and the oily residue was purified by column chromatography to afford the respective N-methyl-N-nosyl-(R)-aminoacyldiazomethane* ***13*** *in 69–89% yield.*

Synthesis of N-Methyl-N-nosyl-3-homoamino Acids (14). General Procedure.[39]

A solution of AgOBz (0.13 mol equiv) dissolved in freshly distilled Et_3N (the volume of Et_3N was adjusted to 1/8 that of the 1,4-dioxane/H_2O solution) was added dropwise to a solution (0.1 M) of the appropriate N-methyl-N-nosyl-(R)-aminoacyldiazomethane ***13*** *in 1,4-dioxane/H_2O (4:1 v/v). The resulting mixture was stirred at room temperature for 20–30 min, until TLC analysis ($CHCl_3$/MeOH 90:10 v/v) of the reaction mixture showed complete conversion of the precursor into the corresponding N-methyl-3-homoamino acid* ***14****. The reaction mixture was filtered and the solvent was removed under vacuum. The residue was dissolved in saturated aqueous $NaHCO_3$ (20 mL) and washed with Et_2O (3 × 10 mL). The aqueous layer was acidified to pH 2 by adding 1 N aqueous HCl (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed once with brine (10 mL) and dried over Na_2SO_4. Evaporation of the solvent under vacuum afforded the respective N-methyl-N-nosyl-3-homoamino acid* ***14*** *in 62–83% yield, without need of chromatography. The N-methyl-N-nosyl-3-homoamino acids were analyzed by GC-MS after their conversion into the corresponding methyl esters by treatment with a CH_2Cl_2 solution of CH_2N_2.*[39]

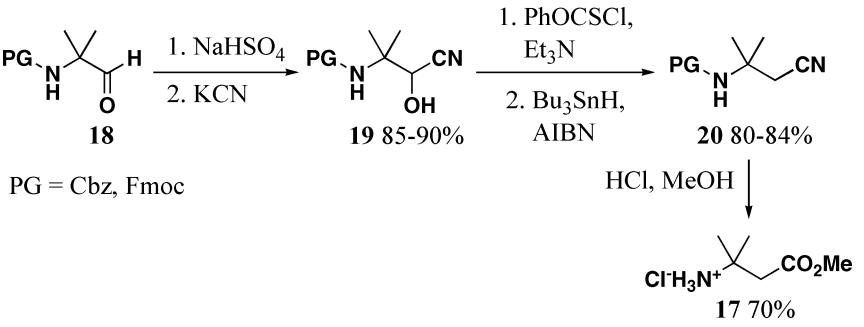
The Arndt-Eistert transformation does have its limitations. There are heightened safety concerns associated with the transport of Diazald and therefore its availability and consequently other homologation methods are being sought. In a recent adaptation to previous work,[40] Caputo *et al.* were able to produce *bis*-deuterated $\beta^{2,2}$-amino acids **16**. The scalable process utilizes β-amino alcohols **15** as precursors, which are iodinated, then the iodo group is displaced with cyanide. The cyano group is finally solvolysed to give the homologated $\beta^{3,2D,2D}$-amino acid ester **16** (*Scheme 5*).[41]



Scheme 5

It was recently demonstrated[42] that the pathway adopted by Caputo *et al*. was not viable in the production of disubstituted-$\beta^{3,3}$-amino acids. Furthermore, it is not practical to access

these residues *via* the Arndt-Eistert homologation. However, access to a disubstituted-$\beta^{3,3}$-amino acid residue **17** was achieved by the initial homologation of an α,α-disubstituted-α-amino aldehyde **18**. The key step in this process exploited a cyanohydrin intermediate **19** in combination with the Barton-McCombie de-hydroxylation (*Scheme 6*).[42]



Scheme 6

N-Benzyloxycarbonyl-3-amino-2-hydroxy-3-methylbutanenitrile (19). Typical Procedure.[42]

*To N-benzyloxycarbonyl-2-amino-2-methylpropan-1-al (**18**, 332 mg, 1.5 mmol) was added an ice-cold solution of saturated $KHSO_4$ (1.2 mmol) and the suspension was allowed to stir vigorously at 5°C for 20 h. To the above solution was added EtOAc (17 mL) and KCN (117 mg, 1.8 mmol) and the mixture was allowed to stir for 20 h at room temperature. The organic layer and the aqueous layer were separated and the organic layer was washed with H_2O (15 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The resulting oil was purified by a short column of silica, eluting with 40% EtOAc-hexane, to furnish N-benzyloxycarbonyl-2-amino-2-hydroxy-3-methylbutanenitrile **19** as a clear colourless oil (335 mg, 90% yield). Found: M^+H, 249.1242; $C_{13}H_{17}N_2O_3$ requires M^+H 249.1239. ν_{max}(KBr)/cm^{-1} 3349 (OH), 3966, 2982, 2944 (CH), 2245 (CN), 1694, 1531, 1262, 1076, 740, 697. ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (5H, s, ArH), 5.81 (1H, bs, NH), 5.57 (1H, s, OH), 4.68–4.66 (1H, m, CHCN), 1.42–1.28 (6H, m, $(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.30 (CO), 135.52 (Aryl C), 128.28, 128.19, 127.98, 127.83, 127.68 (Aryl CH), 118.45 (CN), 68.16 (**C**HCN), 66.85 ($ArCH_2$), 55.47 (**C**$(CH_3)_2$), 23.88, 22.41 (C(**C**$H_3)_2$).*

N-Benzyloxycarbonyl-3-amino-3-methylbutyronitrile (20). Typical Procedure.[42]

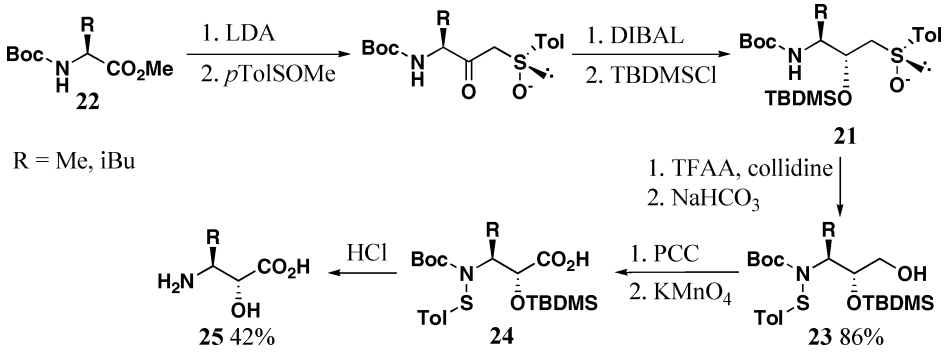
*N-Benzyloxycarbonyl-3-amino-2-hydroxy-3-methylbutanenitrile (**19**, 248 mg, 1 mmol), phenylchlorothionoformate (242 mg, 1.4 mmol), Et_3N (152 mg, 1.5 mmol) and DMAP (12.2 mg, 0.1 mmol) were dissolved in dry MeCN (4 mL) at 0°C in an atmosphere of Ar and the mixture was allowed to stir for 1 h while warming to room temperature. The mixture was diluted with EtOAc (5 mL) and the organic phase was washed with H_2O (3 times). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in $PhCH_3$ and concentrated. The oil, Bu_3SnH (320 mg, 1.1 mmol) and AIBN (16 mg, 0.1 mmol) were dissolved in dry $PhCH_3$ (4 ml) and the solution was deoxygenated by*

bubbling Ar through the solution. The mixture was then heated at reflux for 1 h under an inert atmosphere. The solution was concentrated under reduced pressure and the residue was applied to a silica column eluting with 10–15% EtOAc-hexane, to afford N-benzyloxycarbonyl-3-amino-3-methylbutyronitrile ***20*** *as a clear colourless oil (186 mg, 80% yield). Found: M^+H, 233.1301; $C_{13}H_{17}N_2O_2$ requires M^+H 233.1290. ν_{max}(KBr)/cm^{-1} 3347 (NH), 3035, 2977 (CH), 2248 (CN), 1714 (CO), 1529, 1248, 1090, 740, 697. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (5H, s, ArH), 5.07 (1H, s, NH), 5.04 (2H, s, $ArCH_2$), 2.88 (2H, s, CH_2CN), 1.42–1.29 (6H, m, $(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.53 (CO), 136.04 (Aryl C), 128.40, 128.03, 127.81 (Aryl CH), 117.50 (CN), 66.36 ($ArCH_2$), 50.91 ($\mathbf{C}(CH_3)_2$), 28.36 ($\mathbf{C}H_2CN$), 26.87 ($C(\mathbf{C}H_3)_2$).*

Methyl-3-amino-3-methylbutanoate hydrochloride salt (17). Typical Procedure.[42]

*Dry HCl gas was bubbled through a stirred solution of N-benzyloxycarbonyl-3-amino-3-methylbutyronitrile (****20****, 93 mg, 0.4 mmol) in dry MeOH at 0°C for 2 h. The solution was warmed to room temperature and allowed to stir for 20 h. The solution was concentrated in vacuo and the residue was triturated with Et_2O to afford methyl-3-amino-3-methylbutanoate hydrochloride salt* ***17*** *as a white solid (74 mg, 70% yield). Mp 126–127°C. ^{1}H NMR (300 MHz, D_2O) (rotamers) δ 3.68 (3H, s, OCH_3), 2.70 (2H, s, CH_2), 1.35 (6H, s, $(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.13 (CO), 52.16 (OCH_3), 51.98 ($\mathbf{C}(CH_3)_2$), 42.35 (CH_2), 24.61 ($C(\mathbf{C}H_3)_2$).*[42]

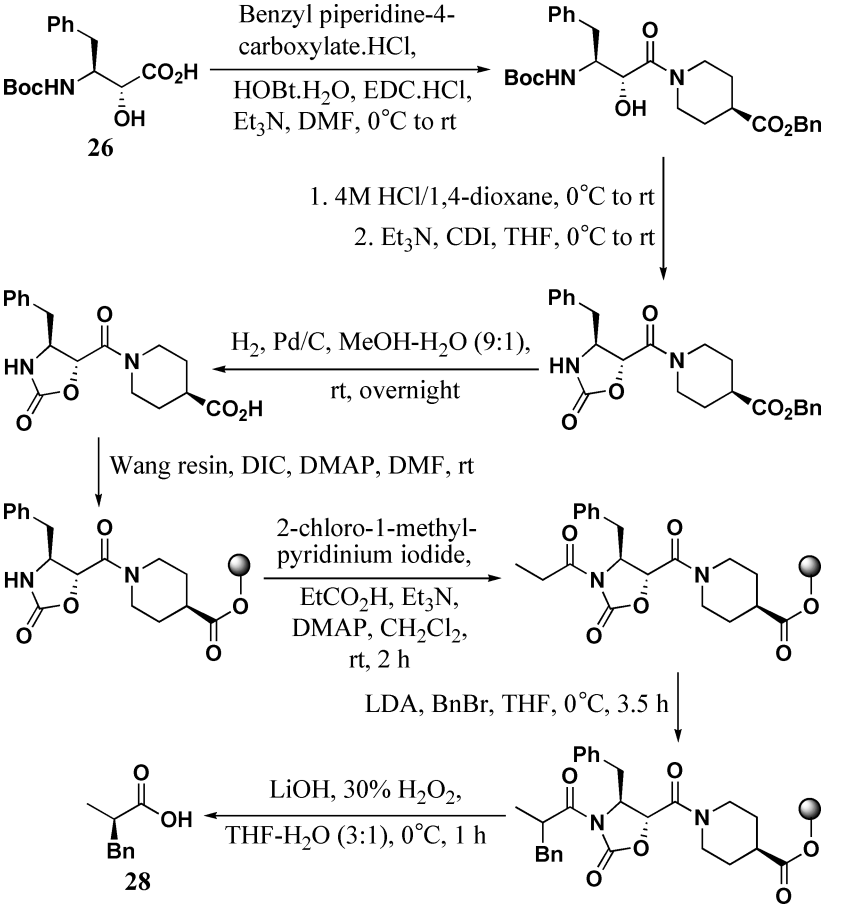
In a different approach, Sanchez-Obregon and colleagues[43] employed a non-oxidative Pummerer reaction. The starting chiral precursors, β-silyloxy-γ-amino sulfoxides **21**, can be obtained easily from α-amino esters **22**. After installation of a β-silyloxy protecting group, the γ-amino sulfoxides **21** then undergo a non-oxidative Pummerer reaction, using trifluoroacetic anhydride and collidine. The resulting sulfenamide-alcohols **23** are then oxidised to the corresponding acid **24** in a two-step process and the protecting groups are acidolysed, to afford the α-hydroxy-β[2,3]-amino acids **25** in overall good yields (*Scheme 7*).[43]



Scheme 7

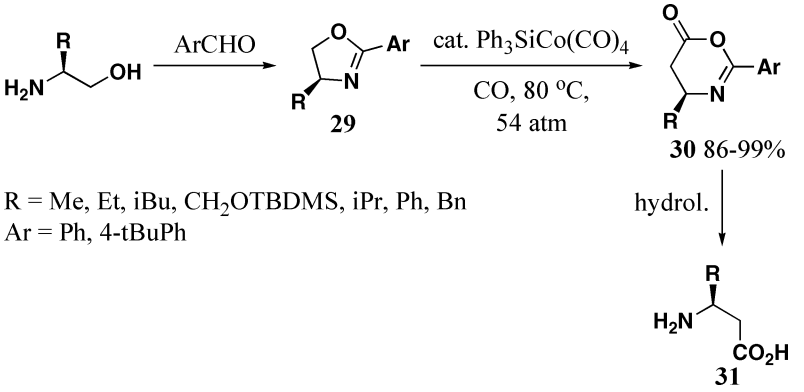
Related α-hydroxy-β[2,3]-amino acids have found use in developments of solid phase chemistry. In recent times, solid phase organic synthesis has been popularly applied for the preparation of organic molecules, especially the preparation of compound libraries

in the process of drug discovery. The Evans' oxazolidinone is one of the most versatile chiral auxiliaries for asymmetric acyl group based transformations. The Evans' oxazolidinone has been used in solid-supports and utilized in asymmetric alkylation, aldol condensation, Diels-Alder and 1,3-dipolar cycloadditions.[44] (2*R*,3*S*)-3-Amino-2-hydroxy-4-phenylbutanoic acid **26** has been used to synthesize a new polymer-supported Evans' chiral auxiliary.[44] These α-hydroxy-$\beta^{2,3}$-amino acids were converted to the corresponding oxazolidinones **27** with a carboxyl group at the 5-position of the ring for anchoring to the solid-support. It was found to be a useful tool for solid-phase asymmetric alkylation with no reduction in stereoselectivity (*Scheme 8*). This handy polymer-supported chiral auxiliary was used in the preparation of a library of chiral α- branched carboxylic acids **28**.[44]



Scheme 8

There are a multitude of different methodologies surrounding carbonylative insertions now appearing in the wider literature. These methods are gaining prevalence in applications to access β-amino acids. One method by Byrne *et al*. describes the carbonylative insertion of a range of α-amino acid derived oxazolines **29** (*Scheme 9*). The oxazinoline insertion products **30** are then hydrolysed to afford a range of β^3-amino acids **31**.[45]



Scheme 9

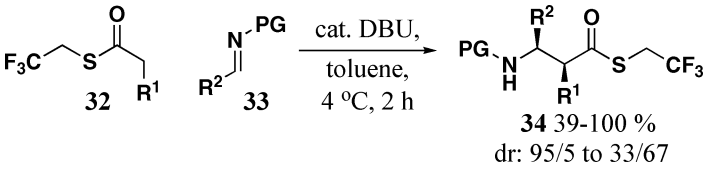
II. Enantioselective Synthesis of β-Amino Acids

1. Organocatalysis Methods

a. Organocatalytic Mannich-type Methods

Recent advances in stereoselective organocatalysis have directly influenced Mannich type β-amino acid syntheses. Both β^3 and $\beta^{2,3}$-amino acids can be produced by this method and there have been some highly stereoselective outcomes.

One such instance was shown by Utsumi and co-workers.[46] They demonstrated that enolisation of a trifluoroethyl thioester **32** using DBU as a catalyst, allowed a Mannich type addition of various *N*-Boc or *N*-Ts protected imines **33**. The resulting $\beta^{2,3}$-amino thioesters **34** were afforded in good to excellent *anti*-diastereoselectivity (*Scheme 10*).[46]



R^1 = 4-ClPh, 4-CF_3Ph, 4-NO_2Ph, Ph, 4-MeOPh, 2-ClPh, 1-Naph, 2-Thienyl, Cl
R^2 = Ph, CO_2Et
PG = Boc, Tosyl, 4-MeOPh

Scheme 10

(S)-2,2,2-Trifluoroethyl 3-(tert-butoxycarbonylamino)-2-(4-chlorophenyl)-3-phenyl-propanethioate (34). Typical Procedure.[46]

*To a cooled solution of thioester (**32**, 23 mg, 0.1 mmol) in $PhCH_3$ (0.5 M) at 0°C, was added imine (**33**, 25 mg, 0.12 mmol) followed by DBU (1.5 mg, 0.01 mmol). After stirring at 4°C for 2–72 h, brine was added and the solution was extracted with EtOAc (3 times). The organic layers were combined, washed with brine, dried by Na_2SO_4, concentrated in*

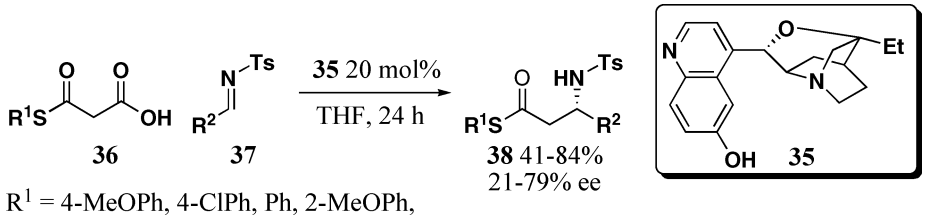
vacuo and purified by flash chromatography (hexane/EtOAc mixture) to afford Mannich reaction product ***34*** *(53 mg, 93% total yield).*

(S)-2,2,2-Trifluoroethyl 3-(tert-butoxycarbonylamino)-2-(4-chlorophenyl)-3- phenyl-propanethioate (34).

Major diastereomer (syn): ^{1}*H NMR (500 MHz, $CDCl_3$): δ 1.26 (s, 9H, $C(CH_3)_3$), 3.31–3.47 (m, 2H, CH_2CF_3), 4.13–4.29 (m, 1H, CHC = O), 4.65–4.85 (m, 1H, NH), 6.26–6.46 (m, 1H, CHNH), 7.23–7.36 (m, 9H, ArH).* ^{13}*C NMR (150 MHz, $CDCl_3$): δ 28.1, 30.7 (q, J = 34.5 Hz), 56.6, 65.4, 80.0, 124.3 (q, J = 276.1 Hz), 127.1, 128.1 128.7, 128.9, 130.5, 132.4, 134.5, 139.3, 154.5, 193.9. HRMS: calcd for $C_{22}H_{23}ClF_3NO_3S$ (MH^+) 474.1118, found 474.1114.*

Minor diastereomer (anti): ^{1}*H NMR (400 MHz, $CDCl_3$): δ 1.35 (s, 9H, $C(CH_3)_3$), 3.40–3.60 (m, 2H, CH_2CF_3), 4.20–4.40 (m, 1H, CHC = O), 5.15–5.30 (m, 1H, NH), 5.40–5.70 (m, 1H, CHNH), 7.20–7.40 (m, 9H, ArH).* ^{13}*C NMR (150 MHz, $CDCl_3$): δ 28.2, 30.9 (q, J = 34.5 Hz), 57.6, 64.2, 80.0, 124.4 (q, J = 275.9 Hz), 126.6, 127.7, 128.6, 129.0, 130.0, 132.6, 134.3, 139.2, 154.8, 193.9. HRMS: calcd for $C_{22}H_{23}ClF_3NO_3S$ (MH^+) 474.1118, found 474.1106.*

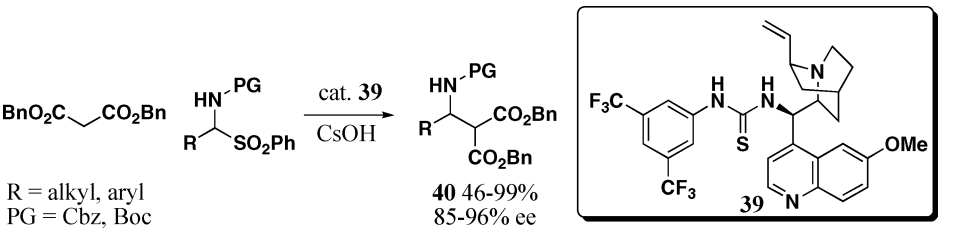
Ricci *et al.*[47] utilized a *Cinchona* alkaloid **35** to catalyse a decarboxylative enolisation of a malonyl thioester **36** (*Scheme 11*). The enolate was allowed to react with various *N*-tosyl-aryl imines **37** to afford the β-amino thioesters **38** with modest enantioselectivity.[47]



R^1 = 4-MeOPh, 4-ClPh, Ph, 2-MeOPh, 4-tBuPh, $PhCH_2CH_2$, nBu, iPr
R^2 = Ph, 4-MeOPh, 1-Naphth, $PhCH_2CH_2$, 2-BrPh, 4-MeOPh

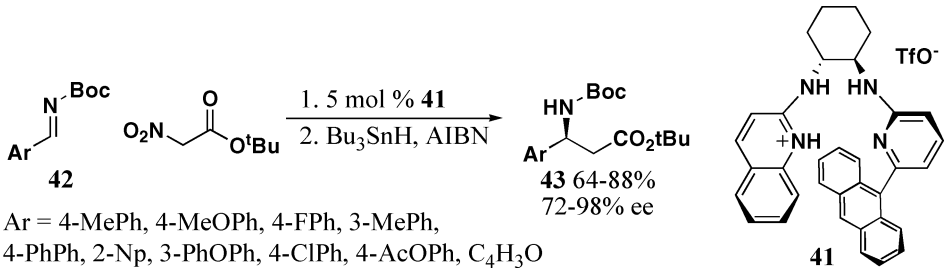
Scheme 11

Song *et al.*[48] were also able to utilize α-amido sulfones to generate *in situ* carbamate protected imines (*Scheme 12*). Using a *Cinchona* alkaloid-thiourea **39** as a catalyst, a malonic ester addition to an imine afforded β-amino bis-ester **40** with excellent enantioselectivity (*Scheme 12*).[48] Although not described, decarboxylative hydrolysis would generate the β^3-amino acid.



Scheme 12

Shen and Johnston[49] used a sterically congested chiral catalyst **41**, in an α-nitro ester addition to *N*-Boc aryl imines **42**. The product was predominately the *syn*-diastereoisomer, with each diastereoisomer possessing a high enantioselectivity. The subsequent α-denitration step was used to great effect to produce a range of β^3-amino esters **43** without any observable loss in enantioselectivity (*Scheme 13*).[49]



Scheme 13

(2S,3R)-tert-Butyl 3-(tert-butoxycarbonylamino)-2-nitro-3-p-tolylpropanoate. Typical Procedure.[49]

*A solution of imine (1.0 equiv) and (**42**) (0.05 equiv) in toluene (0.30 M) was cooled to −78°C and treated with α-nitro tert-butyl acetate (1.1 equiv). The reaction mixture was stirred at -78°C overnight, and then concentrated and directly subjected to purification by flash column chromatography with silica gel.*

nBu_3SnH (2.0 equiv) was added to a solution of the α-nitro-β-amino ester (1.0 equiv) in benzene (0.10 M) followed by AIBN (0.2 equiv). The reaction mixture was stirred at 80°C for 2 h, and then concentrated and purified by flash column chromatography on silica gel.

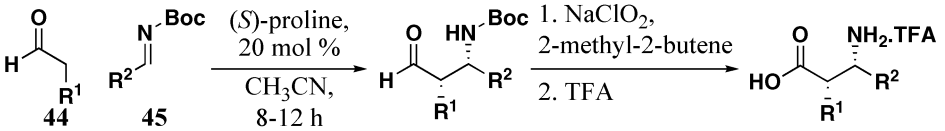
*By the procedure above, the imine (**42**, 35.0 mg, 160 μmol) provided a nitro ester after flash column chromatography (10–15% ethyl acetate in hexanes) as a white solid (55.5 mg, 91%), which was determined to be 88% ee (each diastereomer) and 2:1 (syn:anti) dr by chiral HPLC analysis (Chiralcel AD-H, 10% iPrOH/hexanes, 1 mL/min, tr (syn, major) = 17.1 min, tr (syn, minor) = 7.4 min, tr (anti, major) = 12.8 min, tr (anti, minor) = 8.8 min). Rf = 0.45 (20% EtOAc/hexanes); IR (neat) 3453, 2981, 2933, 1746, 1722, 1565, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 2:1 mixture of diastereomers) major: δ 7.23–7.13 (m, 4H), 6.14 (br d, J = 8.1 Hz, 1H), 5.65 (br d, J = 8.6 Hz, 1H), 5.59 (br s, 1H), 2.31 (s, 3H), 1.50 (s, 9H), 1.43 (s, 9H); minor: δ 7.23–7.13 (m, 4H), 5.95 (br s, 1H), 5.71 (br s, 1H), 5.29 (br d, J = 5.4 Hz, 1H), 2.33 (s, 3H), 1.41 (s, 9H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 2:1 mixture of diastereomers) major: δ 161.5, 154.9, 138.2, 133.5, 129.7, 125.9, 92.2, 85.8, 80.4, 53.8, 28.4, 27.8, 21.1; minor: δ 161.8, 154.9, 138.4, 133.4, 129.7, 126.7, 89.6, 85.2, 80.4, 54.5, 28.3, 27.6, 21.1; HRMS (ESI): Exact mass calculated for $C_{19}H_{28}N_2NaO_6$ $[M^+Na]^+$ 403.1845; found 403.1855.*

(S)-tert-Butyl 3-(tert-butoxycarbonylamino)-3-p-tolylpropanoate (43). Typical Procedure.[49]

*Following the general procedure, the nitroacetate (28.6 mg, 75.2 μmol, 88% ee) provided the β-amino ester **43** after flash column chromatography (10–15% EtOAc in hexanes) as a*

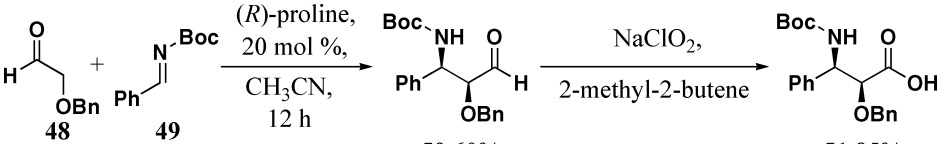
white solid (22.6 mg, 90%), which was determined to be 88% ee by chiral HPLC analysis (Chiralcel AD-H, 10% iPrOH/hexanes, 1 mL/min, tr (major) = 9.0 min, tr (minor) = 9.6 min). $[\alpha]_D^{20}$ −24.5 (c 1.30, CHCl3); Rf = 0.48 (20% EtOAc/hexanes); mp 98–100°C; IR (neat) 3381, 2978, 2924, 1708, 1506, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 5.39 (br s, 1H), 5.02 (br s, 1H), 2.73–2.65 (br m, 2H), 2.31 (s, 3H), 1.41 (s, 9H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.3, 155.1, 138.5, 137.0, 129.3, 126.2, 81.1, 79.5, 51.3, 42.3, 28.5, 28.0, 21.1; HRMS (ESI): Exact mass calculated for $C_{19}H_{29}NNaO_4$ $[M^+Na]^+$ 358.1994; found 358.1995.

(*S*)-Proline, is a common organocatalyst and it was used by Yang and co-workers[50,51] to affect a Mannich reaction of a range of alkyl aldehydes **44** with *N*-Boc-aryl imines **45**. The resulting disubstituted $\beta^{2,3}$-amino aldehydes **46** were obtained by filtration and in both excellent *syn*-diastereoselectivity and enantioselectivity. The aldehydes were easily oxidised to their respective $\beta^{2,3}$-amino acids **47** (*Scheme 14*).[50,51]



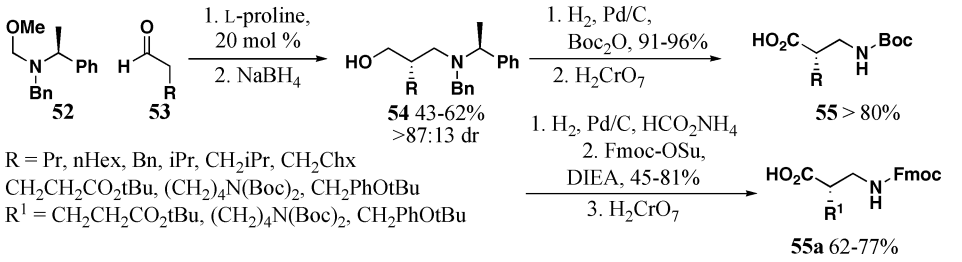
Scheme 14

In a modification of the work of Yang *et al.*,[50,51] Dziedzic and co-workers demonstrated various *O*-protected α-oxyaldehydes **48** can also undergo a (*S*)-proline catalysed Mannich addition to an *N*-Boc aryl imine **49**. The β-amino aldehydes **50** were obtained in excellent diastereoselectivity and enantioselectivity and could then be oxidised to obtain the α-hydroxy $\beta^{2,3}$-amino acids 51 (*Scheme 15*).[52]



Scheme 15

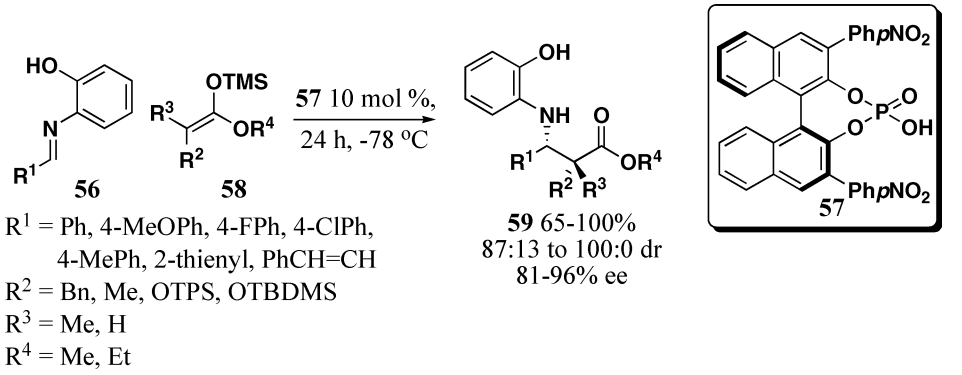
In a different approach, Chi and co-workers[53] utilized (*S*)-proline, in the production of β^2-amino acids (*Scheme 15*). An imine, generated *in situ* from a *N,O*-acetal **52** derived from *N*-benzyl-(*R*)-methylbenzylamine and formaldehyde, was shown to react with a variety of aliphatic aldehydes **53**. The β^2-amino aldehydes were formed in high diastereoselectivity, however to avoid epimerisation at the α-center, sodium borohydride was employed to reduce the aldehyde *in situ* to the corresponding alcohol **54**. The resulting *N,N-bis*-benzyl-γ-amino alcohols **54** were then subjected to hydrogenolysis in the presence of Boc anhydride and the resulting alcohols were oxidised to afford the enantiopure *N*-Boc- β^2-amino acids



Scheme 16

55; similary, hydrogenolysis of **54** followed by treatment with Fmoc-OSu and oxidation afforded **55a** (*Scheme 16*).[53]

An interesting approach to access both β^3- and $\beta^{3,2,2}$-amino acids by Itoh *et al.*[54,55] uses an *N*-2-hydroxyphenyl aldimine **56** in combination with a BINOL phosphonic acid catalyst **57**. It was proposed coordination of the phosphonic acid to the *N*-2-hydroxyphenyl aldimine induced a zwitterionic transition state. The activated imine was allowed to undergo a Mannich-like addition of various *O*-TMS ketenes **58**. The resulting *N*-2-hydroxyphenyl β^3-amino esters **59** were obtained in low to high enantioselectivity depending on the steric bulk of the aldimine substituent. The *N*-2-hydroxyphenyl moiety was neatly removed by *O*-alkylation, followed by oxidation (*Scheme 17*).[54,55]

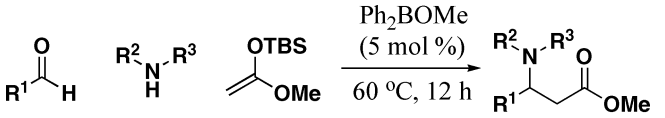


Scheme 17

Boronic acids are finding increased use in organocatalysis. This has been attributed to their mild Lewis acid properties. Tanaka *et al.*[56] used this property to their advantage in a Mannich reaction to form various *N*,*N*-disubstituted-β^3-amino acids **60**. A diphenyl boronate catalysed the formation of an imine using various *N*,*N*-dialkyl amines **61** with aryl and alkyl aldehydes **62**. The imine formation was followed by attack of a silyl ketene acetal **63** to produce *N*,*N*-dialkyl β^3-amino esters **60** (*Scheme 18*).[56]

b. Organocatalytic Conjugate Addition Methods

Conjugate additions of amines to α, β-unsaturated carbonyl systems have been widely used in the synthesis of β-amino acids.[1,8,25,26,30,31] However, producing residues in a



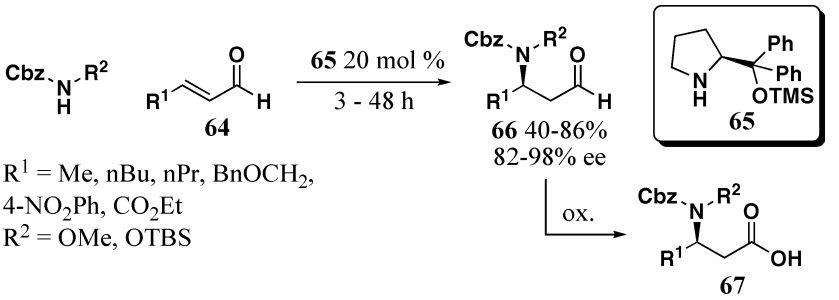
62 **61** **63** **60** 74-91%

R^1 = aryl, alkyl
R^2, R^3 = alkyl, aliphatic

Scheme 18

stereoselective fashion remains a challenge. Recently organocatalytic methods have provided significant advances in this area.

Proline-like organocatalysts remain at the forefront of these advances. Ibrahem *et al.*[57] have performed a study using various proline-derived catalysts, in *O*-methyl- or *O*-silylhydroxylamine conjugate additions, to a variety of substituted α, β-unsaturated aldehydes **64**. The outcome of the study was that the diarylprolinol **65** was the most efficient at catalysing highly enantioselective conjugate additions. The resulting β-amino aldehydes **66** were oxidised to the acid and hydrogenated to cleave the *O*-methyl-hydroxylamine functionality to give rise to the desired highly enantiopure β^3-amino acids **67** (*Scheme 19*).[57]



64

R^1 = Me, nBu, nPr, $BnOCH_2$, 4-NO_2Ph, CO_2Et
R^2 = OMe, OTBS

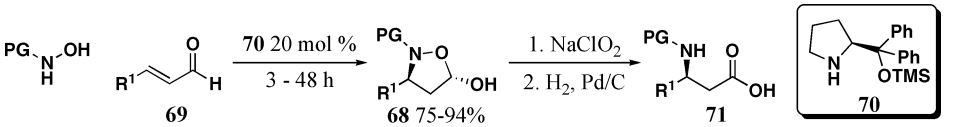
66 40-86%
82-98% ee

65

67

Scheme 19

In an extension of this work, Ibrahem *et al.*,[58,59] used Boc-*N*-hydroxylamine to perform a conjugate addition (*Scheme 20*). The conjugate addition product then spontaneously cyclised to the 5-hydroxyisooxazolidine **68**. A variety of alkyl and aryl substituted α,β-unsaturated aldehydes **69** were shown to undergo this process, using a diarylprolinol catalyst **70**, in excellent enantioselectivity. The ensuing oxidation and hydrogenolysis produced a variety of β^3-amino acids **71** in excellent yields.[58,59]



69

PG = Cbz, Boc
R^1 = Ph, 4-ClPh, 4-BrPh, 4-CNPh, 4-O_2NPh, 2-naphthyl, nBu, nPr, CO_2Et

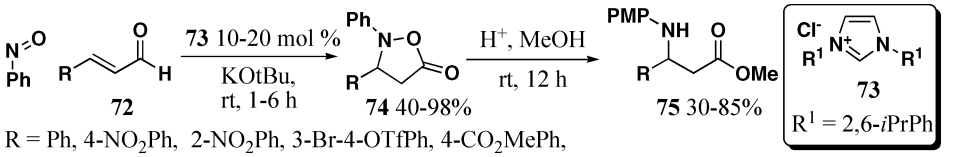
68 75-94%
91-99% ee

71

70

Scheme 20

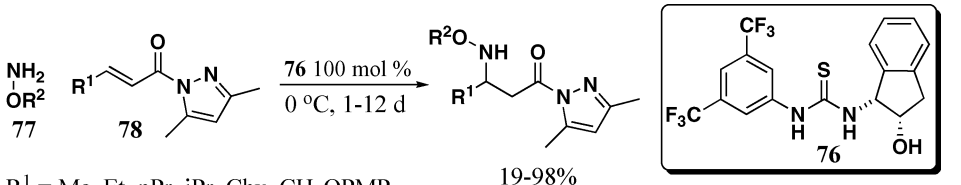
5-Hydroxyisooxazolidinones are the outcome of a reaction between nitrosobenzene and a cinnamaldehyde **72** (*Scheme 21*). The carbene catalyst **73** used, activates the unsaturated system towards nucleophilic attack by nitrosobenzene. The nitroxide formed, can then attack the carbonyl group intramolecularly, leading to the isoxazolidinone **74**. In the same pot the hydroxylamine bond is cleaved by acidic hydrolysis and a Bamberger-like rearrangement takes place, neatly producing *N*-*p*-methoxyphenyl protected β^3-amino acid esters **75**, in good to excellent yields (*Scheme 21*).[60]



R = Ph, 4-NO_2Ph, 2-NO_2Ph, 3-Br-4-OTfPh, 4-CO_2MePh, 6-CO_2MePh, 4-CNPh, 4-CF_3Ph, C_6F_5, 3,5-F_2Ph, C_4H_9, CO_2Et

Scheme 21

Sibi and Itoh[61] are continuing to develop catalysts for producing β-amino acids with high enantiopurity. In one instance, a readily available thiourea catalyst **76** was used in a conjugate addition of *O*-benzyl hydroxylamine **77** to a selection of substituted α,β-unsaturated pyrazole amides **78**. The key to the high enantioselectivity of this process is a series of hydrogen bonds the catalyst forms with both the pyrazole amide and the approaching nucleophile (*Scheme 22*).[61]



R^1 = Me, Et, nPr, iPr, Chx, CH_2OPMP, CO_2Et, Ph
R^2 = TBDMS, Ph_2CH, Bn

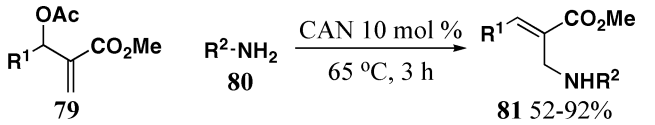
Scheme 22

2. Asymmetric Michael Additions

A novel example of an asymmetric conjugate addition involves substrate chirality transfer. This method exclusively produces dehydro-β^3-amino esters.

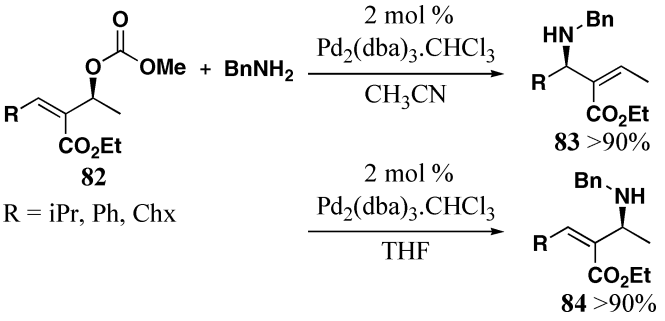
One such method was described recently by Paira *et al.*,[62] utilizing Baylis-Hillman adducts **79**. The ceric ammonium nitrate-mediated regioselective addition of amines **80** to the Baylis-Hillman acetate **79** resulted in dehydro-β^3-amino esters **81** predominantly in the *E* geometry (*Scheme 23*).[62]

Cardillo and co-workers[63] similarly demonstrated a regioselective allylic amination can be performed using palladium catalysis. The addition of benzylamine to a selection of enantiopure Baylis-Hillman carbonates **82** or acetates in acetonitrile resulted in excellent transfer of chirality and regioselectivity to the reaction products **83**. Interestingly, in some



R^1 = aryl
R^2 = alkyl, aryl

Scheme 23



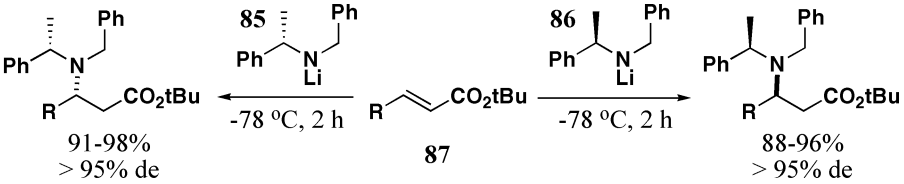
Scheme 24

instances using THF as solvent produced the dehydro-$\beta^{3,2}$-amino esters **84** with the reverse regioselectivity (*Scheme 24*).[63]

a. Conjugate Additions Using Chiral Scaffolds

Amine additions to α,β-unsaturated systems have been widely used in β-amino acid synthesis.[1,8,11,13,15,16,21,26,30,31] Recent improvements in stereoselectivity are largely due to the enormity of the range of chiral auxiliaries that are now readily available. The chiral auxiliaries can be appended to either the encroaching nucleophile or the accepting electrophile.

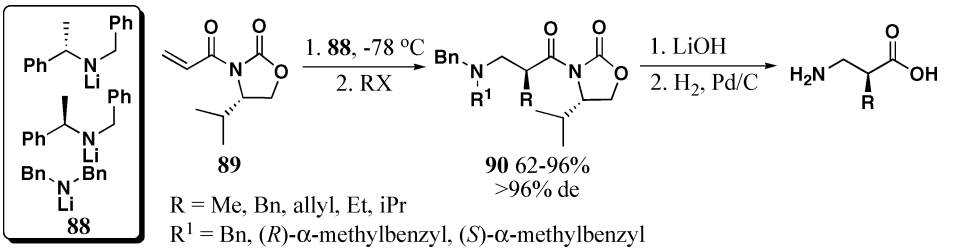
In a classic approach Davies *et al.*[64] used chiral lithium dibenzylamides **85** or **86** in additions to various β-substituted conjugated esters **87**. The stereochemical outcome of the reaction is dependent on the chirality of the benzylamide used. Davies and co-workers demonstrated this classical addition reaction can be undertaken in a parallel synthesis with excellent yields and diastereoselectivity (*Scheme 25*).[64]



R = Me, iBu, nHept, 4-MeOPh, 3-MeOPh, 2-MeOPh, 3,5-MeOPh, 3,4-MeOPh, 2,4-MeOPh, Ph, 4-PhPh, Piperon-3-yl, 3-BnOPh, 4-BnOPh, 3,4-BnOPh

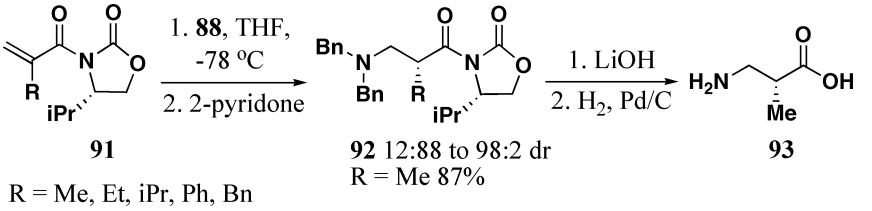
Scheme 25

In ongoing studies by Davies and colleagues,[65] lithium dibenzylamides **88** were reacted with the *N*-acryloyl SuperQuat framework **89**. The resulting enolate was then trapped by addition of alkyl halides. The stereochemical outcome of this reaction was not dependent on the chirality of the particular dibenzylamide **88** used, but was reliant on the SuperQuat moiety. Excellent yields and diastereoselectivities of the adducts **90** were obtained from a variety of alkyl halides used (*Scheme 26*).[65]



Scheme 26

A similarly impressive result was obtained when an α-substituted *N*-acryloyl SuperQuat scaffold **91** was reacted with lithium dibenzylamide. It was observed that the reagent used to quench the reaction has a profound effect on the stereochemical outcome of the reaction. Under the optimised conditions, 2-pyridone gave both excellent yields and diastereoselectivities of the chiral adduct **92**. The dibenzyl and SuperQuat moieties were then easily removed to produce enantiopure β^2-amino acid **93** (*Scheme 27*).[65]

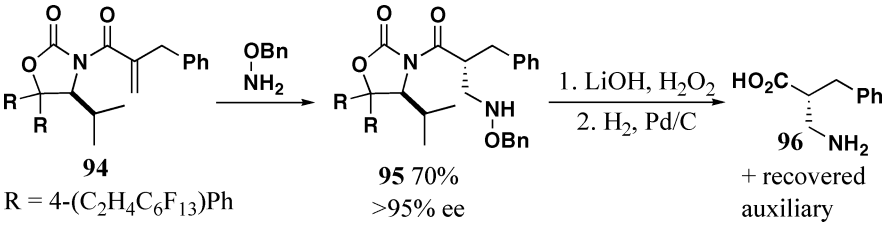


Scheme 27

In a modification of the work by Davies, Vogtle and co-workers[66] used a similar auxiliary, a 5,5-diphenyl-2-oxazolidinone **94** to which a perfluoro alkane tag was attached. This enabled the use of fluorous solid-phase extraction, allowing efficient purification of the crude reaction products **95** and **96** and easy recovery of the auxiliary. The tagged *N*-acryloyl-5,5-diphenyl-2-oxazolidinone **94** was reacted with *O*-benzyl hydroxylamine in stereoselective fashion. The following auxiliary and hydroxylamine cleavage gave the β^2-amino acid **96** in up to 25 g quantities in enantiopure form (*Scheme 28*).[66]

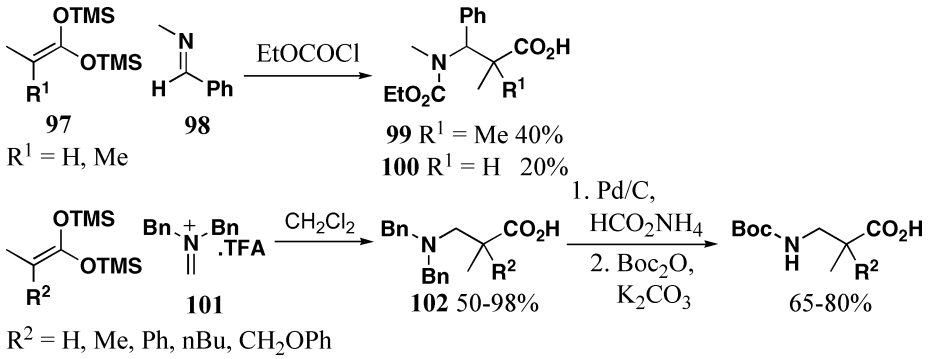
b. Mannich Type Additions Using Chiral Scaffolds

Chiral scaffolds are much used in Mannich type additions for the synthesis of β-amino acids. Over a series of publications Moumne and co-workers[67–69] developed a Reformatsky reaction, whereby nucleophilic enolate species, generated *in situ*, react with disubstituted iminium salts. In earlier studies, bis(*O*-trimethylsilyl) ketene acetals **97** were reacted with an



Scheme 28

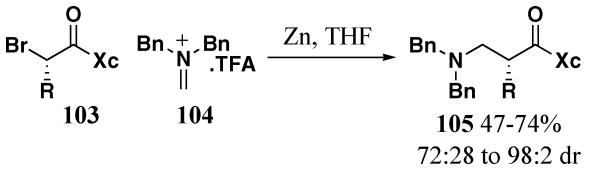
imine **98** in the presence of ethyl chloroformate. This produced substituted $\beta^{2,3}$-amino acids **99** and **100** in low yields and little diastereoselectivity was observed. In a modification of this procedure, disubstituted iminium salt **101** was used in place of the imine. This resulted in a marked increase in yields of $\beta^{2,3}$-amino acids **102**. The use of the dibenzyl iminium salt **101** allowed the resultant *N*,*N*-dibenzyl $\beta^{2,3}$- and $\beta^{2,2,3}$-amino acids **102** to be easily deprotected (*Scheme 29*).[67,68]



Scheme 29

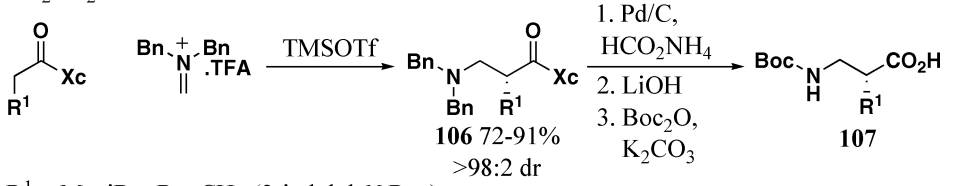
In an extension of this work, various substituted α-bromoacids were coupled to (+)-camphorsultam to form the bromoacyl sultams **103**. The enolate was then formed by addition of zinc dust, and this was then reacted with the dibenzyl iminium salt **104**. The sultam auxiliary gave good diastereoselectivity for the products **105** depending on the steric bulk of the α-substituent. Other auxiliaries were tried but no improvement in diastereoselectivity was observed. Interestingly, the replacement of zinc, with trimethylsilyl triflate to form the enolate resulted in large improvements in both yields and diastereoselectivity of the adducts **106**. The dibenzyl protection and sultam were removed to afford the β^2-amino acids **107** in their enantiopure form (*Scheme 30*).[69]

Sulfinimines, with their inherent chirality, have been used to good effect in the stereoselective synthesis of β-amino acids. In a recent advance, Davis and Song[70] used various substituted sulfinimines **108** to react with a series of enolates. The enolate of *N*-methoxy-*N*-methylpropyl amide **109** resulted in the formation of the *syn*-α-methyl β-amino Weinreb-amides **110** (*Scheme 31*). Good to excellent diastereoselectivity was observed, depending on the steric bulk of substituents and the conditions used. The *N*-sulfinyl moiety and the amide were removed by hydrolysis to give access to the disubstituted $\beta^{2,3}$-amino acids **111** in high yields (*Scheme 31*).[70]



103 **104** **105** 47-74%
72:28 to 98:2 dr

R = Me, iBu, Bn, CH_2-(3-indolyl-*N*-Boc), CH_2CO_2tBu



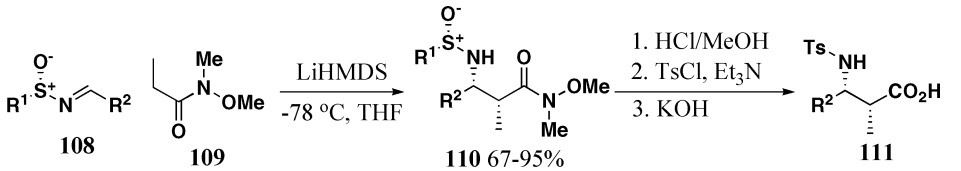
106 72-91%
>98:2 dr

107

R^1 = Me, iBu, Bn, CH_2-(3-indolyl-*N*-Boc), CH_2CO_2tBu, C_6H_{13}, $Br(CH_2)_4$, *N*-Bn-3-methylene

Xc = (+)-camphorsultam

Scheme 30



108 **109** **110** 67-95%
>80:17 dr

111

R^1 = 2,4,6-Me_3Ph, 2,4,6-$i Pr_3$Ph

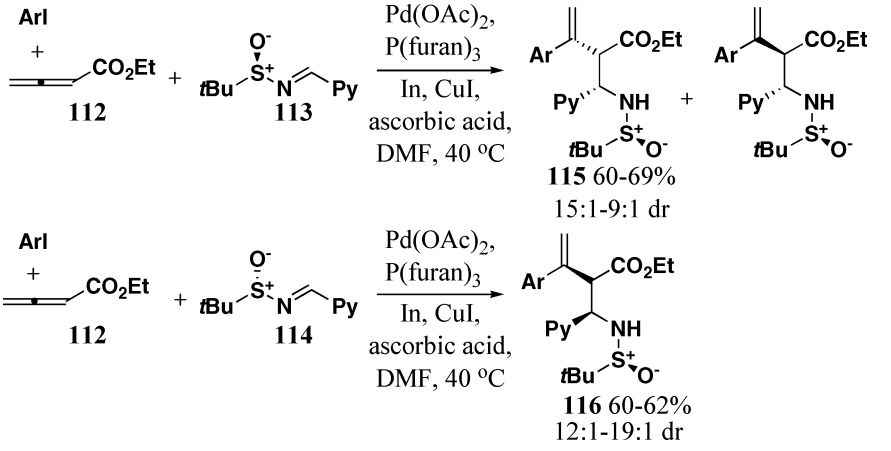
R^2 = Et, Ph

Scheme 31

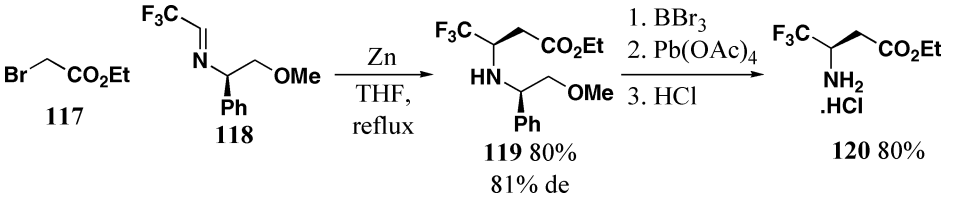
Grigg *et al.*[71] have also exploited the sulfinimine scaffold in an elegant synthesis of functionalised $\beta^{2,3}$-amino acids. The formation of the reacting nucleophile was performed *in situ*, by an oxidative palladium-mediated aryl iodide addition to allene acetate **112**. The allylic-palladium species formed, was then transmetallated with indium creating a reactive nucleophile. The reactive indium species then undergoes a Reformatsky-like addition to the substituted sulfinimine **113** or **114**. High diastereoselectivities and good yields were observed across a variety of aryl substituents. This multifaceted reaction allows access to a collection of unusual disubstituted $\beta^{2,3}$-amino acids **115** and **116** (*Scheme 32*).[71]

A phenylglycinol auxiliary was used by Dos Santos and colleagues[72] in the synthesis of trifluoromethyl β^3-amino acids. The zinc mediated addition of α-bromo ethylacetate **117** to the (*R*)-phenylglycinol trifluoromethyl aldimine **118** resulted in a β^3-amino ester **119** in good diastereoselectivity and yield. The mixture of diastereoisomers were separated chromatographically and subjected to a three-step removal of the auxiliary and ester. The process afforded the enantiopure trifluoromethyl β^3-amino acid **120** in excellent yield (*Scheme 33*).[72]

By varying the imine chiral entity to a sterically encumbered *N*-phosphonyl group, Han and co-workers,[73] were able to perform a Mannich type reaction to afford β^3-amino esters **121** (*Scheme 34*). The *N*-phosphonyl imine **122** was reacted with ester enolates

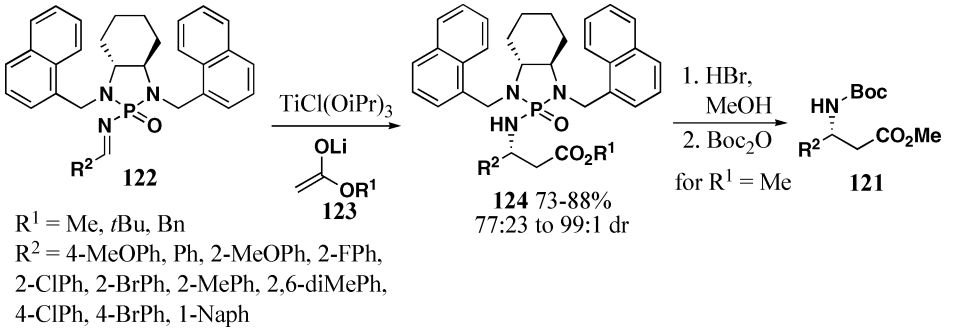


Scheme 32



Scheme 33

123, formed *in situ* in the presence of triisopropoxy titanium (IV) chloride. The Lewis acid promoter was observed to enhance stereoselectivity. A variety of *N*-phosphonyl aryl substituted β^3-amino esters **124** were produced with high diastereoselectivity and in good yields. The *N*-phosphonyl group can be readily hydrolysed to afford the β^3-amino ester **121** with high enantiopurity (*Scheme 34*).[73]



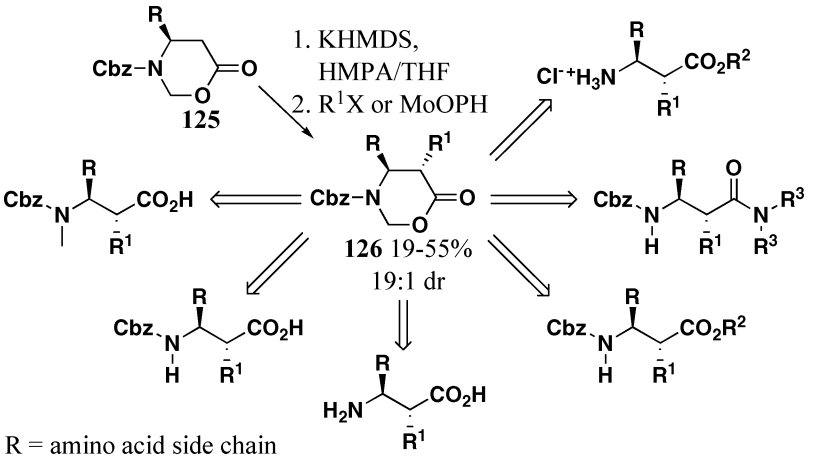
Scheme 34

3. Enolate Additions

Enolate chemistry has been widely used to access β-amino acids.[1,8,11,13,15,16,20–22,24,25,28–31] These methods generally use chiral synthons to induce stereoselectivity.

However, an alternative approach exploited a pre-existing scaffold, used to produce *N*-methyl-β-amino acids. The 1,3-oxazinan-6-one scaffold **125** was studied in a variety of enolate reactions. The best conditions for α-alkylation employed KHMDS in tandem with HMPA, to give the products **126** (R^1 = Me) with excellent *anti*-selectivity, in good yields.[74]

Similar conditions were used for hydroxylation at the 5-position of the 1,3-oxazinan-6-one **125**. A number of electrophilic hydroxylation reagents were trialed. It was found that MoOPH was the most successful hydroxylation reagent, also providing the desired residues **126** (R^1 = OH) with excellent *anti*-selectivity. Such is the versatility of the scaffold, the α-substituted 1,3-oxazinan-6-ones can be subjected to a range of conditions to produce a number of disubstituted-$\beta^{2,3}$-amino acid variants (*Scheme 35*).[74]



Scheme 35

(4S,5S)-N-Benzyloxycarbonyl-4-isopropyl-5-methyl-6-oxo-1,3-oxazinane (126) and (4S)-N-Benzyloxycarbonyl-4-isopropyl-5,5-dimethyl-6-oxo-1,3-oxazinane. Typical Procedure.[74]

*(4S)-N-Benzyloxycarbonyl-4-isopropyl-6-oxo-1,3-oxazinane (**125**, 138 mg, 0.5 mmol) was dissolved in dry THF (4 mL) and HMPA (1 mL) and the solution was cooled to –78°C under an Ar atmosphere. KHMDS (0.5 M in $PhCH_3$, 0.525 mmol) was added dropwise and the solution was left to stir at –78°C for 40 min. MeI (5 mmol) was added and stirring was continued for 4 h at –78°C. The solution was then allowed to warm to –15°C and it was then quenched with saturated NH_4Cl solution (5 mL). The solution was diluted with EtOAc (20 ml) and washed with H_2O (20 ml). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give an oil. The oil was subjected to column chromatography eluting with 5–20% EtOAc-hexane, to afford the starting material **125** (29 mg, 21% recovery), (4S,5S)-N-benzyloxycarbonyl-4-isopropyl-5-methyl-6-oxo-1,3-oxazinane **126** (71 mg, 49% yield), Found: M^+H, 292.1548; $C_{16}H_{21}NO_4$*

*requires M^+H 292.1549. $[\alpha]_D^{20}$ +119.3 (c, 0.56 in CH_2Cl_2). ν_{max}(NaCl)/cm^{-1} 2968 (CH), 1754, 1712 (CO), 1408, 1258, 1133, 1000, 698. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (5H, s, ArH), 5.89 (1H, bs, H-2A), 5.16 (2H, s, $ArCH_2$), 4.93 (1H, d, J 10.7 Hz, H-2B), 3.80 (1H, bs, H-4), 2.71 (1H, dq, J 6.7 and 8.6 Hz, H-5), 2.02–1.94 (1H, m, NCHC**H**), 1.31 (3H, d, J 6.7 Hz, C**H**$_3$CHCO), 1.01 (3H, d, J 5.7 Hz CHC**H**$_3$), 0.94 (3H, d, J 6.8 Hz, CHC**H**$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.76, 155.43 (CO), 135.42 (Aryl C), 128.58, 128.42, 128.17 (Aryl CH), 72.97 (C-2), 68.34 ($ArCH_2$), 61.00 (C-4), 38.06 (C-5), 31.38 (NCH**C**H), 20.36 (**C**H_3CHCO), 16.99, 15.23 (CH(**C**$H_3)_2$). And (4S)-N-benzyloxycarbonyl-4-isopropyl-5,5-dimethyl-6-oxo-1,3-oxazinane was isolated as an oil (26 mg, 17% yield). Found: M^+H, 306.1700; $C_{17}H_{23}NO_4$ requires M^+H 306.1705. $[\alpha]_D^{20}$ +17.0 (c, 0.28 in CH_2Cl_2). ν_{max}(KBr)/cm^{-1} 3033, 2967 (CH), 1747, 1713 (CO), 1392, 1246, 1101, 1011, 747, 698. ^{1}H NMR (300 MHz, $CDCl_3$) (323K) δ 7.33 (5H, s, ArH), 5.92 (1H, bs, H-2A), 5.26–5.07 (3H, m, $ArCH_2$ and H-2B), 4.00 (1H, bs, H-4), 2.12–2.05 (1H, m, NCHC**H**), 1.31–1.29 (6H, m, $C(CH_3)_2$), 1.04–0.88 (6H, m, $CH(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$) (323K) δ 174.27, 154.79 (CO), 135.89 (Aryl C), 128.64, 128.45, 128.25, 128.14, 127.97 (Aryl CH), 75.08 (C-2), 68.17 ($ArCH_2$), 63.66 (C-4), 43.08 (C-5), 29.60 (NCH**C**H), 27.80, 21.98, 21.42, 18.46 (4 × CH_3).*

(2R,3S)-N-Benzyloxycarbonyl-3-aminomethyl-2,4-dimethylpentanoic Acid. Typical Procedure.[74]

*(4S,5S)-N-Benzyloxycarbonyl-4-isopropyl-5-methyl-6-oxo-1,3-oxazinane (**126**, 293 mg, 1 mmol) was dissolved in CH_2Cl_2 (min. vol.) and CF_3CO_2H (50:50, v:v). Et_3SiH (349 mg, 3 mmol) was added and the solution was stirred for 48 h. $PhCH_3$ (15 mL) was added to the solution and it was then evaporated in vacuo, and this process was repeated 3 times to remove any trace of CF_3CO_2H. The residue was taken up in Et_2O (30 mL) and extracted with saturated $NaHCO_3$ (20 mL × 3). The aqueous layer was adjusted to pH 2 with dilute HCl solution, and extracted with EtOAc (25 mL × 3). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The resulting residue was subjected to column chromatography using a solvent system of EtOAc and MeOH to afford (2R,3S)-N-benzyloxycarbonyl-3-aminomethyl-2,4-dimethyl-pentanoic acid as a clear colourless oil (190 mg, 65% yield), (Found: M^+H, 294.1705. $C_{16}H_{23}NO_4$ requires M^+H 294.1705). $[\alpha]_D^{20}$ −29.0 (c, 0.15 in CH_2Cl_2). ν_{max}(NaCl)/cm^{-1} 3032, 2966 (CH), 1733, 1698, 1761 (CO), 1456, 1340, 1162, 697. ^{1}H NMR (300 MHz, $CDCl_3$) (323K) δ 7.31 (5H, s, ArH), 5.12 (2H, s, $ArCH_2$), 4.04 (1H, bs, NCH), 2.96–2.85 (1H, m, CHCO), 2.81 (3H, s, NCH_3), 2.17–2.10 (1H, m, NCHC**H**), 1.21–1.15 (3H, m, CH_3), 1.05–0.96 (3H, m, CH_3), 0.88–0.84 (3H, m, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers)δ 179.3, 157.5, 157.11 (CO), 137.14, 136.9 (Aryl C), 128.43, 127.97, 127.86, 127.59 (Aryl CH), 67.41, 67.23 ($ArCH_2$), 64.50 (NCH), 40.43 (NCH_3), 31.08 (CHCO), 28.60, 28.40 (NCH**C**H), 20.30 (CH_3), 19.47, 19.25 (CH_3), 14.78, 14.64 (CH_3).*[74]

(4S,5S)-N-Benzyloxycarbonyl-5-hydroxy-4-isopropyl-6-oxo-1,3-oxazinane (126). Typical Procedure.[74]

*(4S)-N-Benzyloxycarbonyl-4-isopropyl-6-oxo-1,3-oxazinane (**125**, 138 mg, 0.5 mmol) was dissolved in dry THF (4 mL) and the solution was cooled to –78°C under an Ar atmosphere.*

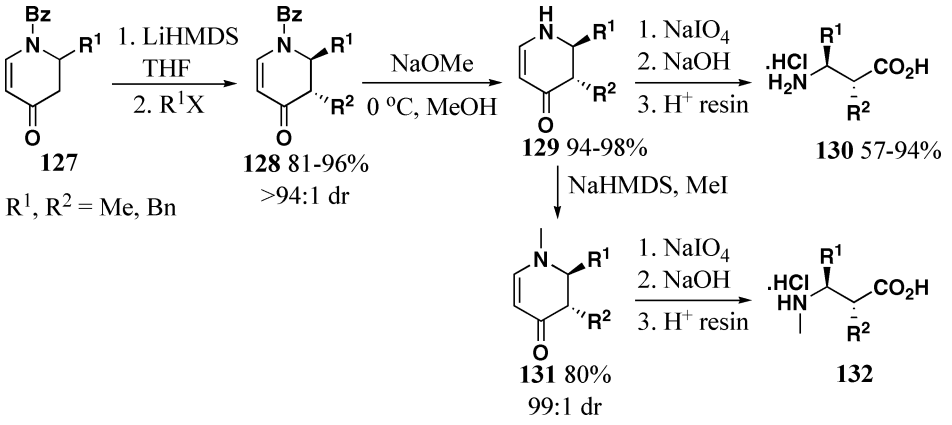
NaHMDS (0.4 M in hexanes, 0.525 mmol) was added dropwise and with stirring the solution was allowed to warm to –50°C over 40 min. MoOPH (0.65 mmol) was added in six portions over 30 min, while the solution was allowed to warm to –40°C. The reaction was maintained at this temperature for 2 h. The solution was then allowed to warm to –30°C and was quenched with saturated Na_2SO_3 solution (5 mL). The solution was diluted with EtOAc (20 ml) and it was then washed with H_2O (20 ml). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure give in an oily residue. The oil was subjected to column chromatography eluting with 10–25% EtOAc-hexane, to afford starting material ***125*** *(10 mg, 7% recovery) and (4S,5S)-N-benzyloxycarbonyl-5-hydroxy-4-isopropyl-6-oxo-1,3-oxazinane* ***126*** *as a clear colourless oil (64 mg, 44% yield). Found: M^+H, 294.1341; $C_{15}H_{20}NO_5$ requires M^+H 294.1341. $[\alpha]_D^{20}$ +71.5 (c, 1.1 in CH_2Cl_2). ν_{max}(NaCl)/cm^{-1} 3446 (OH), 2965 (CH), 1768, 1714 (CO), 1410, 1254, 1105, 984, 746, 698. ^{1}H NMR (300 MHz, $CDCl_3$) (323K) δ 7.34 (5H, s, ArH), 5.94 (1H, d, J 10.8 Hz, H-2A), 5.17 (2H, s, $ArCH_2$), 4.88 (1H, d, J 10.8 Hz, H-2B), 4.33 (1H, d, J 8.5 Hz, H-5), 3.87 (1H, dd, J 5.6 and 8.0 Hz, H-4), 3.42 (1H, bs, CHO**H**), 2.16–2.07 (1H, m, NCHC**H**), 1.05 (1H, d, J 6.9 Hz, CHC**H**$_3$), 0.99 (1H, d, J 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) (323K) δ 173.51, 154.94 (CO), 135.33 (Aryl C), 128.54, 128.40, 128.10 (Aryl CH), 72.79 (C-2), 68.60 ($ArCH_2$), 68.03 (C-5), 62.03 (H-4), 32.10 (NCH**C**H), 18.56, 18.10 ((CH_3)$_2$).*

(2R,3S)-N-Benzyloxycarbonyl-3-aminomethyl-2-hydroxy-4-methylpentanoic Acid. Typical Procedure.[74]

*(4S,5S)-N-Benzyloxycarbonyl-5-hydroxy-4-isopropyl-6-oxo-1,3-oxazinane (**126**, 293 mg, 1 mmol) was dissolved in CH_2Cl_2 (min. vol.) and CF_3CO_2H (50:50, v:v). Et_3SiH (349 mg, 3 mmol) was added and the solution was stirred for 48 h. $PhCH_3$ (15 mL) was added to the solution and it was then evaporated in vacuo, and this process was repeated 3 times to remove any trace of CF_3CO_2H. The residue was taken up in Et_2O (30 mL) and extracted with saturated $NaHCO_3$ (20 mL × 3). The aqueous layer was adjusted to pH 2 with dilute HCl solution, and extracted with EtOAc (25 mL × 3). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The resulting residue was subjected to column chromatography using a solvent system of EtOAc and MeOH to afford (2R,3S)-N-benzyloxycarbonyl-3-aminomethyl-2-hydroxy-4-methyl-pentanoic acid as a clear colourless oil (186 mg, 63% yield). Found: M^+H, 296.1497; $C_{15}H_{21}NO_5$ requires M^+H 296.1498. $[\alpha]_D^{20}$ −1.3 (c, 0.39 in CH_2Cl_2). ν_{max}(NaCl)/cm^{-1} 3432 (OH), 2965, 2876 (CH), 1729, 1673 (CO), 1456, 1312, 1138, 975, 736, 697. ^{1}H NMR (300 MHz, $CDCl_3$) (323K) δ 7.33 (5H, s, ArH), 5.15 (2H, s, $ArCH_2$), 4.44–4.36 (1H, m, CHCO), 3.75 (1H, bs, NCH), 2.97–2.90 (3H, m, NCH_3), 2.43–2.30 (1H, m, NCHC**H**), 0.95 (3H, d, J 6.5 Hz, CH_3), 0.90 (3H, d, J 6.5 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) (323K) δ 173.96, 158.31 (CO), 136.26 (Aryl C), 128.56, 128.19, 127.72 (Aryl CH), 73.50, 72.51 (**C**HCO), 68.56, 67.86 ($ArCH_2$), 34.86 (NCH_3), 26.41 (NCH**C**H), 20.21, 19.53 ((CH_3)$_2$).*[74]

In a similar type of approach, Ege and Wanner[75] used racemic dihydropyridones **127** as a template for enolate chemistry. Using LiHMDS as base and various alkyl halides, the enolate chemistry performed, produced excellent *anti*-diastereoselectivity and excellent yields of the α-substituted dihydropyridones **128**. Subsequent deprotection of the *N*-benzoyl group with sodium methoxide proceeded smoothly. The *N*H-dihydropyridone **129** was then

oxidised to the corresponding disubstituted $\beta^{2,3}$-amino acid **130** in high yields. It was also demonstrated the *N*H-dihydropyridone **129** could be *N*-methylated. However, oxidation of the resulting dihydropyridone **131** to the desired *N*-methyl-β-amino acid **132** did not proceed as expected (*Scheme 36*).[75]



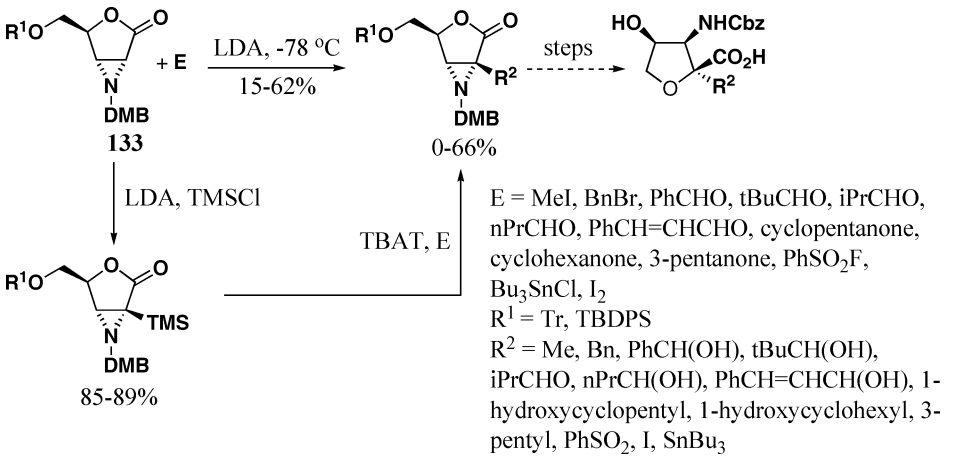
Scheme 36

Valle *et al.*[76] demonstrated that D-ribonolactone-derived 2,3-aziridino-γ-lactones **133** could be used as a platform to perform enolate chemistry. Initial enolate experiments using standard enolate forming conditions gave significant self-condensation of the lactone. To circumvent this problem the electrophile and the aziridine were added to an LDA solution. This resulted in good yields of the addition of a variety of electrophiles to the enolate. Using aldehydes as electrophiles did not produce any noteworthy diastereoselection. The enolates were also trapped using trimethylsilyl chloride. The proceeding reaction used TBAT (tetrabutylammonium triphenyldifluorosilicate) to generate the enolate which was then reacted with various electrophiles. Unfortunately, no increase in yield was seen using this two-step process compared with the direct enolate approach. Further studies are ongoing to ascertain whether nucleophilic aziridine ring opening is practical in producing highly functionalised β-amino acids (*Scheme 37*).[76]

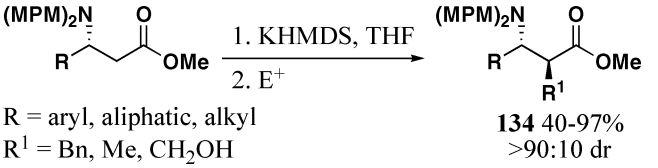
The use of sterically congested or chiral *N*-protecting groups of β^3-amino esters has been widely used in enolate chemistry. Capone and colleagues[77] demonstrated the effectiveness of *N*,*N*-bis-4-methoxybenzyl protection in production of $\beta^{2,3}$-amino esters **134** (*Scheme 38*). The enolate formed was reacted with a multitude of different electrophiles. The $\beta^{2,3}$-amino esters **134** were obtained in good to excellent yields with excellent *anti*-diastereoselectivity (*Scheme 38*).[77]

Recently, there has been an increase in the number of enolate chemistries performed to produce β^2-amino acids. The use of chiral sterically hindered amide auxiliaries has seen marked increases in stereoselectivity.

One such instance was used by Tessier and co-workers.[78] They appended a Fox auxiliary to the acid group of *N*,*N*-dibenzyl β-alanine to give adduct **135** in excellent yields. Although the *cis* and *trans* Fox adducts were isolated it was observed the *trans* gave rise to the highest diastereoselectivity. Using NaHMDS as a base and various electrophiles, excellent yields and diastereoselection in the products **136** resulted. The auxiliary was recovered

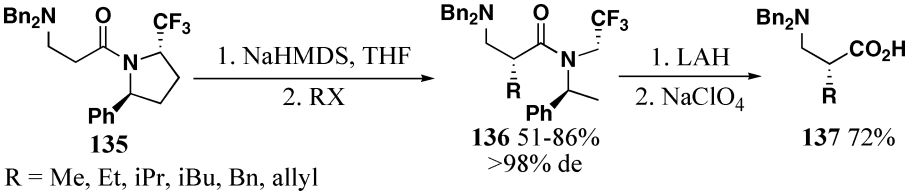


Scheme 37



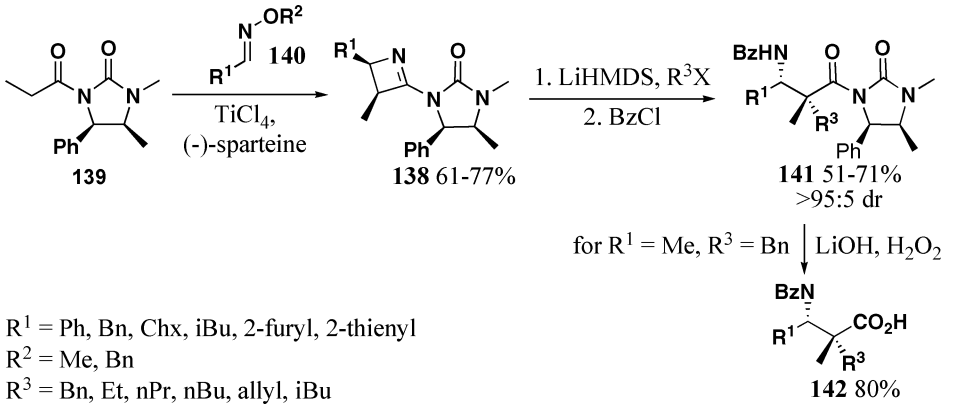
Scheme 38

after cleavage using LAH to produce the corresponding β^2-amino aldehyde. The aldehyde was then oxidised to afford the enantiopure *N*-protected β^2-amino acid **137** (*Scheme 39*).[78]



Scheme 39

An interesting approach by MacNevin *et al.*[79] utilized azetidines **138** affixed to an ephedrine derived chiral imidazolidin-2-one auxiliary. The formation of the azetidine proceeded by a titanium chloride mediated ring closure of an α-substituted amide **139** with either various isocyanates or *O*-methyl oximes **140**. Both electrophilic reagents gave modest to excellent yields, however little diastereoselectivity was observed. The *cis*-azetidine **138** was then subjected to standard enolisation conditions and treated with numerous alkyl halides. Excellent diastereoselectivity and good yields of the expected adducts were obtained. The *trans*-azetidine gave appreciably lower yields and diastereoselectivity. The α-alkylated azetidines were then ring opened by the addition of benzoyl chloride affording



Scheme 40

141 and the auxiliary was hydrolysed to produce the $\beta^{2,2,3}$-amino acid **142** or ester in good yields across two steps (*Scheme 40*).[79]

4. Enantioselective Hydrogenation and Reduction Methods

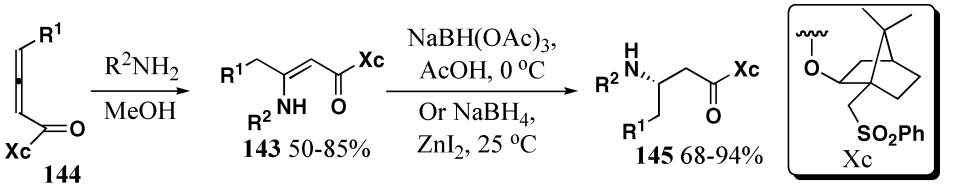
The number of now commercially available chiral auxiliaries and catalysts has had a direct influence on the conduct of enantioselective reductions of conjugate systems for the synthesis of β-amino acids.

a. Reduction Methods Using Chiral Scaffolds

Chiral auxiliaries in reductive methodology direct the hydride source to the least hindered face in order in induce stereoselectivity.

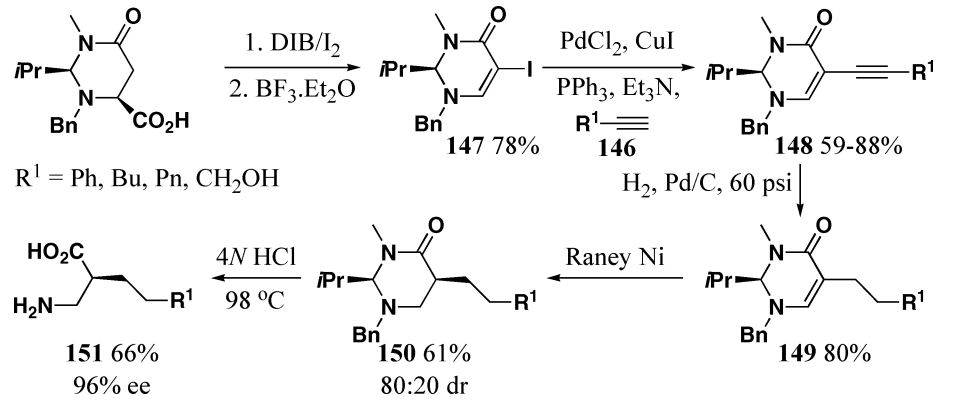
A classic approach is the use of camphorsulfonyl type auxiliaries. Pinho e Melo *et al.*,[80] used this to great effect in the synthesis of β^3-amino acids. The starting enantiopure precursor β-enamine esters **143** were prepared by a nucleophilic addition of a benzylamine or allyl amine to either the (1*R*)-(−)- or (1*S*)-(+)-10-phenylsulfonylisobornyl allenoates **144**. The β-enamine esters were then subjected to reductive amination conditions using sodium triacetoxyborohydride or zinc borohydride to give the β-amino esters **145**. The chelation of either the zinc or the boronate that was suggested to occur in the transition state, gives excellent chiral induction. The (1*R*)-(−)-10-phenylsulfonylisobornyl β-enamine esters **143** gave β^3-amino esters **145** exclusively with *S* configuration whereas the (1*S*)-(+)-10-phenylsulfonylisobornyl β-enamine esters led to β^3-amino esters **145** exclusively with *R* configuration (*Scheme 41*).[80]

Another highly utilized scaffold is the 2-substituted dihydropyrimidinone. Using this scaffold, Diaz-Sanchez and colleagues[81] performed a reduction of various 5-substituted dihydropyrimidinones to access β^2-amino acids. A Sonogashira reaction of various alkynes **146** to a 5-halo-2-substituted dihydropyrimidinone **147** was used in the production of the precursors **148**. The alkyne moiety was then reduced using palladium mediated hydrogenation affording dihydropyrimidinones **149**. The following Raney nickel reduction reduced the dihydropyrimidinone system to the pyrimidinone **150** with modest



R^1 = H, Me, *i*Pr, *t*Bu, Bn
R^2 = Bn, PMB, allyl

Scheme 41



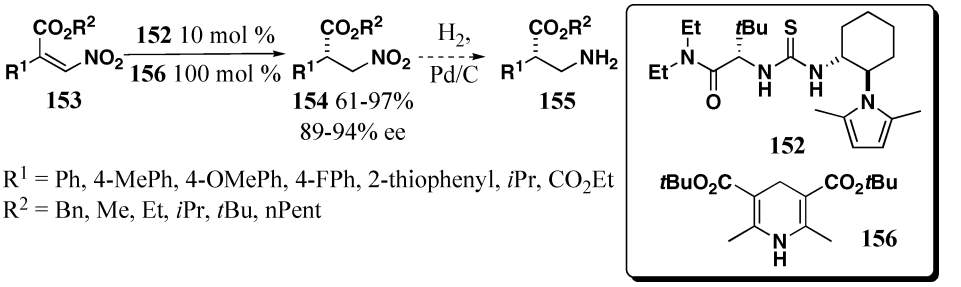
Scheme 42

diastereoselectivity. The diastereomers were separated and under optimised hydrolysis conditions, the β^2-amino acid **152** was produced in high enantiopurity (*Scheme 42*).[81]

b. Reduction Methods Using Chiral Catalysts

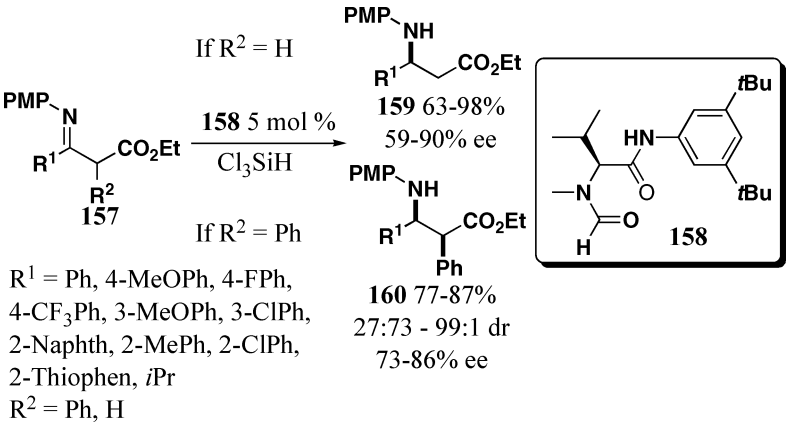
Organocatalysis has been mentioned in this review, but not in regards to organocatalytic reduction of unsaturated systems. Martin and co-workers,[82] describe a fine example of such an organocatalytic transformation. Using a highly optimised Jacobson type-thiourea organocatalyst **152** from their previous work, a Hantzsch ester-mediated conjugate reduction of a variety (*Z*)-nitro acrylates **153** was performed. The saturated β-nitro esters **154** were obtained with high (*R*)-enantioselectivity and yield. In further studies it was discovered that the geometry of the starting nitroacrylate was critical to the enantiopurity of the product. Starting with a (*E*)-nitroacrylate, high (*S*)-enantioselectivity was achieved for the enantiomers of **154**. The saturated nitro esters **154** could then be hydrogenated to afford the β^2-amino esters **155** in high yield (*Scheme 43*).[82]

Another example of organocatalytic reduction was performed by Malkov *et al.*[83] The starting *N*-PMP β-imino β -substituted esters **157**, were reduced using trichlorosilane and the organocatalyst Sigamide **158**, with high enantioselectivity for the products **159** and **160**. However, reproducibility was problematic, due to the Bronsted acid mediated equilibrium between the *E* and *Z* enamines of **157**. It was found the addition of one equivalent of acetic acid, gave reproducible selectivity and high yields of the β^3-amino ester **159**. Similarly a



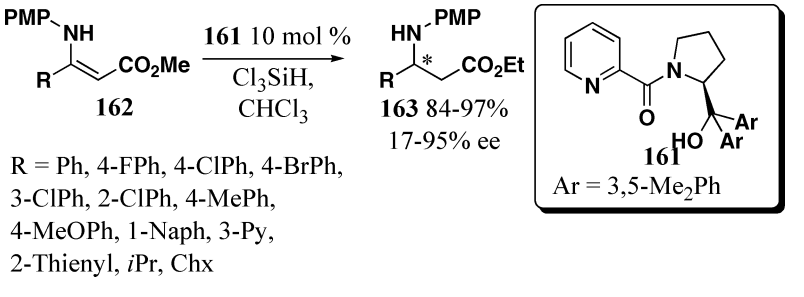
Scheme 43

range of enamine α,β-disubstituted esters also gave the $\beta^{2,3}$-amino esters **160** in excellent *syn*-diastereoselectivity, with high enantioselectivity and yields (*Scheme 44*).[83]



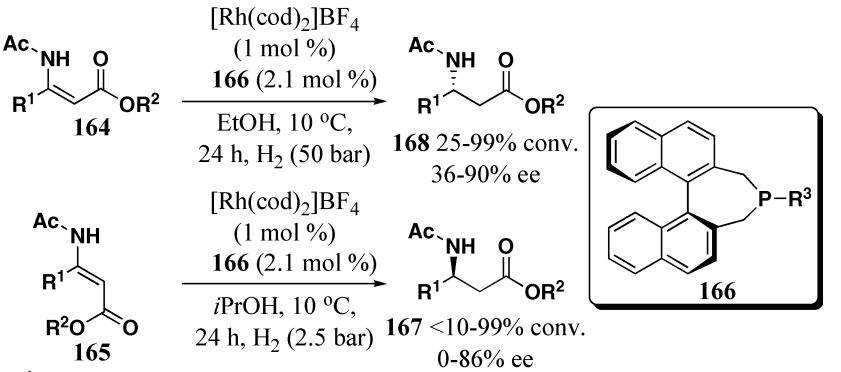
Scheme 44

In a similar reduction method, Zheng *et al.* utilized a prolinol organocatalyst **161**. *N*-PMP enamino β-substituted esters **162** were reduced using trichlorosilane, to produce the β^3-amino esters **163** in high yield with moderate to excellent enantioselectivity (*Scheme 45*).[84]



Scheme 45

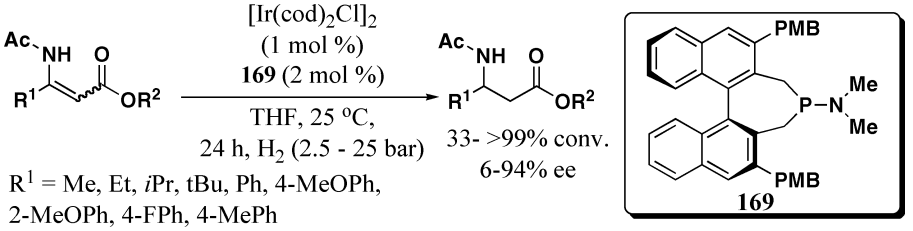
The use of phosphine ligands in the reductive synthesis of β-amino acids is becoming increasingly popular. This is due to more of these ligands now being commercially available.



R^1 = Me, Et, *i*Pr, Ph
R^2 = Me, Et, *i*Pr
R^3 = *i*Pr, *t*Bu, Ph, 4-FPh, 3,5-Me_2Ph, 4-MeOPh, 2-MeOPh, 3-MeOPh, 3,4-MeO_2Ph

Scheme 46

Enthaler *et al.*[85,86] are involved in ongoing improvements in the selectivity of reactions using phosphine ligands. In one study β-acetamidoacrylates **164** and **165** were subject to a high pressure hydrogenation, using a dinaphthyl-phosphine ligand in combination with a rhodium catalyst (*Scheme 46*). The enantioselectivity of the process was dependent on a number of factors, including solvent type, pressure and temperature. The starting enamine geometry was crucial for the stereochemical outcome of the reaction. The (*E*)-β-acetamido acrylates **165** and (*Z*)-β-acetamido acrylates **164** produce the (*R*)-β^3-amino esters **167** and the (*S*)-β^3-amino esters **168**, respectively, in moderate to high enantioselectivity (*Scheme 46*).[85] In a variation of this study, an iridium catalyst was used in combination with a phosphoramidite ligand **169**. High enantioselectivity was obtained, but once again the selectivity was highly dependent on the reaction conditions (*Scheme 47*).[86]

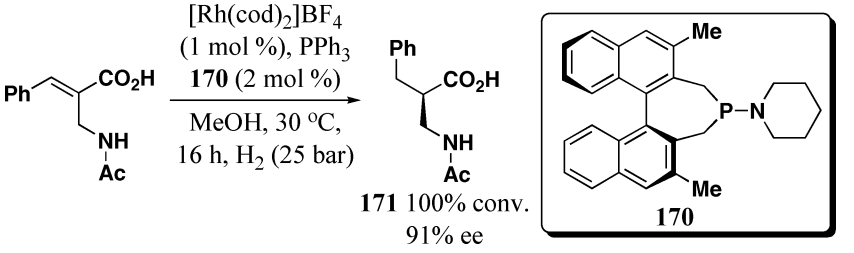


R^1 = Me, Et, *i*Pr, tBu, Ph, 4-MeOPh, 2-MeOPh, 4-FPh, 4-MePh
R^2 = Me, Et, *i*Pr

Scheme 47

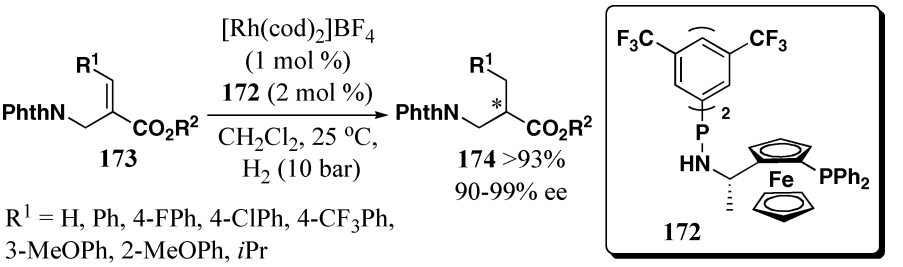
In a similar study Hoen and co-workers[87] used β-acetamido acrylic acids as precursors for rhodium catalysed hydrogenations. In the study, the phosphoramidite ligand **170** was formed *in situ*. This allowed the optimisation study to be conducted in a high throughput

manner. Under the optimised reaction conditions the β^2-amino acids **171** were produced in quantitative yields with high enantiopurity (*Scheme 48*).[87]



Scheme 48

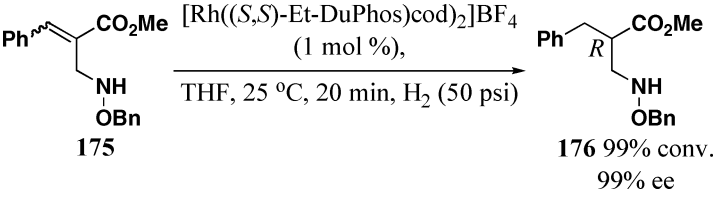
Deng and co-workers[88] used a series of BoPhoz-type ligands *e. g.* **172**, in the rhodium-catalyzed hydrogenation of a variety of (*E*)-β-substituted α-phthalimidomethyl acrylates **173**. Under the optimised reaction conditions excellent yields and enantioselectivities of the β^2-amino esters **174** were achieved. The phthalimide protection was subsequently hydrolysed to afford the (*S*)-β^2-amino acid (*Scheme 49*).[88]



R^1 = H, Ph, 4-FPh, 4-ClPh, 4-CF_3Ph, 3-MeOPh, 2-MeOPh, *i*Pr
R^2 = Me, Et

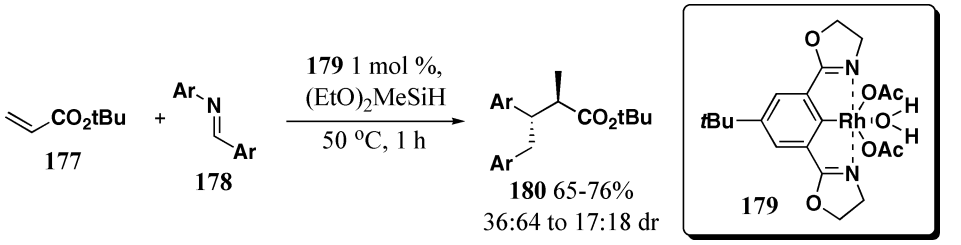
Scheme 49

In another study Qiu *et al.*,[89] utilized an array of readily available phosphine ligands in combination with either ruthenium or rhodium. The asymmetric reduction of the *a*-aminomethylacrylates **175** was optimised by varying reaction conditions such as temperature, solvent and pressure. In contrast, to the previously mentioned studies, under the conditions described, a mixture of *E*/*Z* α-aminomethylacrylates could be used to produce one enantiomer of the ester **176**. The chirality of the phosphine ligand governed the stereochemical outcome (*Scheme 50*).[89]



Scheme 50

In a different approach, Nishiyama *et al.*[90] used a conjugate reduction of an acrylate **177** to perform a Mannich like addition to an aldimine **178**, promoted by a rhodium-bis (oxazolinyl)phenyl catalyst **179** and an alkoxyhydrosilane. Under the best conditions in the optimisation study, a sterically bulky substituted aldimine resulted in high yields and excellent *anti*-diastereoselectivity of the disubstituted $\beta^{2,3}$-amino ester **180** (*Scheme 51*).[90]

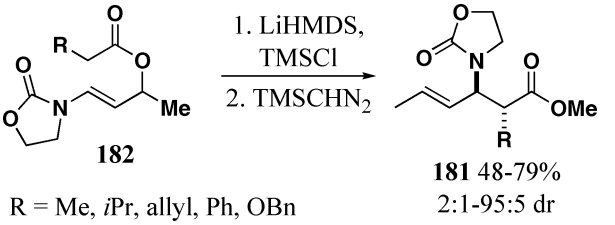


Scheme 51

5. Rearrangement Methods

One of the original syntheses of an α-amino acid was by a Curtius rearrangement.[91] Since then, great advances have been made in the development of rearrangement reactions, particularly in the synthesis of β-amino acids.

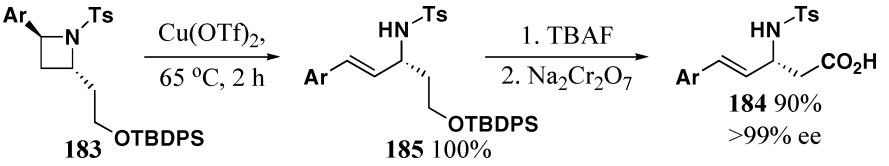
In an interesting approach, an Ireland–Claisen [3,3]-sigmatropic rearrangement was utilized, by Ylioja and co-workers,[92] to access highly functionalised $\beta^{2,3}$-amino esters **181**. A three-step process allowed access to an assortment of substituted propionate precursors **182** in reasonable yields. Optimisation of the rearrangement reaction and subsequent esterification allowed the resulting $\beta^{2,3}$-amino esters **181** to be isolated in good yields with moderate to high *anti*-diastereoselectivity (*Scheme 52*).[92]



Scheme 52

Ghorai and co-workers[93] recently developed a ring opening rearrangement of 2-aryl-azetidines **183** for the synthesis of allyl substituted β^3-amino acids **184**. The starting chiral *N*-tosyl 2-aryl azetidines **183** were made simply from enantiopure phenylglycinol. The azetidine was then subjected to ring opening with cuprous triflate, affording the allyl amine **185** in excellent yield. The silyl protecting group was removed and oxidation of the alcohol gave the enantiopure unsaturated β^3-amino acid **184** in excellent yield (*Scheme 53*).[93]

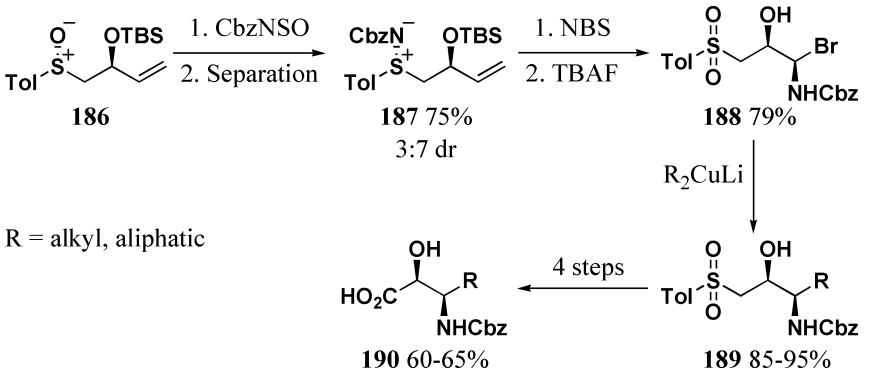
In the key step to highly functionalised $\beta^{2,3}$-amino acids, Raghavan *et al.*[94] employed an oxidative intramolecular transfer. The readily accessed chiral sulfoxide **186** was reacted with



Ar = Ph, 4-MeOPh, 4-ClPh, 2-ClPh, 3-BrPh

Scheme 53

N-sulfinyl benzylcarbamate to afford the *N*-Cbz sulfinilimine **187**. The *N*-Cbz-sulfinilimine **187** was then treated with NBS and the following intramolecular rearrangement resulted in a bromo carbamate **188**. The bromo substituent was then utilized to attach a number of biologically relevant side chains using organocuprate chemistry. A protective group strategy was required for the transformation of the sulfone **189** to an aldehyde *via* a Pummerer intermediate. Subsequent Pinnick oxidation of the aldehyde yielded the functionalised diastereopure $\beta^{2,3}$-amino acids **190** in overall good yields (*Scheme 54*).[94]



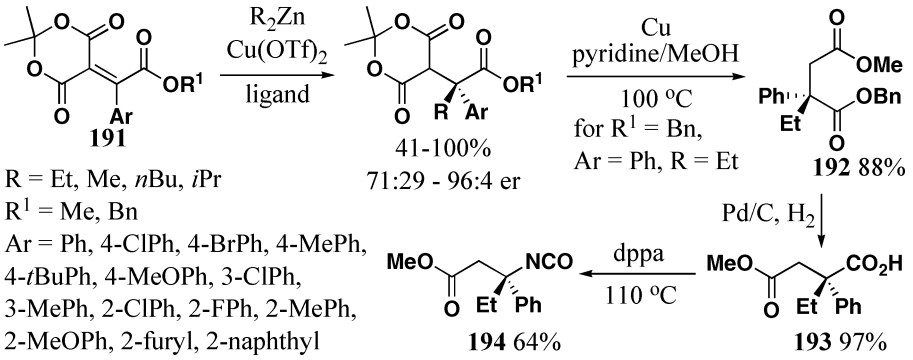
Scheme 54

A Curtius rearrangement of a chiral succinate was used in a key step by Wilsily and Fillion,[95] to allow access to $\beta^{3,3}$-amino acids. A variety of chiral succinates were produced by a copper catalysed organo zincate 1,4-addition to an alkylidenated Meldrum's acid **191**. The chiral phosphoramidite ligands used afforded the addition products with high enantioselectivities and yields. A decarboxylative Meldrum's acid ring opening and hydrogenolysis of a benzyl ester **192** provided a succinic acid **193**. The acid **193** was then subjected to a Curtius rearrangement to produce the disubstituted $\beta^{3,3}$-amino ester derivative **194** (*Scheme 55*).[95]

III. Residue Specific Synthesis and Applications

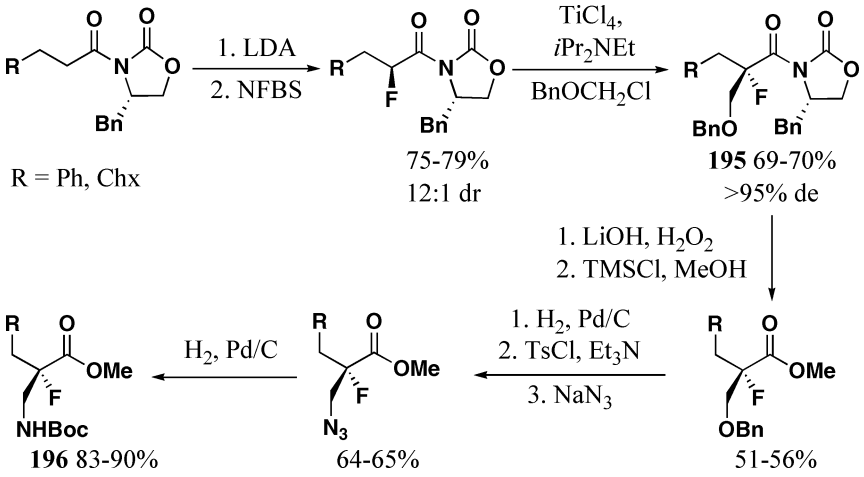
1. Halo-β-amino Acids

In a classical approach to fluorinated-β^2-amino acids, Abell *et al.*[96] utilized enolate chemistry. An Evans type auxiliary induced good diastereoselectivity when *N*-fluorobenzene sulfonimide (NFBS) was used as the electrophile. Subsequent Lewis acid mediated



Scheme 55

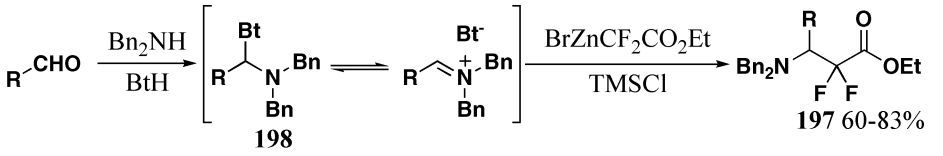
alkylation of the α-centre using benzyl chloromethyl ether, afforded the β-benzyl ether **195** with excellent stereochemical control and in good yield. Conversion of the benzyl ether **195** into the β-amino moiety in a few steps provided the fluoro-β^2-amino esters **196** in high yield (*Scheme 56*).[96]



Scheme 56

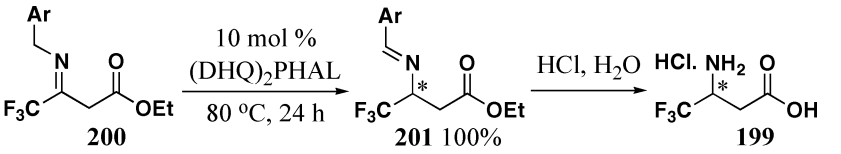
In an adaption of their previous work Boyer *et al.*[32] used the Reformatsky reaction to access a variety of difluoro $\beta^{3,2,2}$-amino esters **197**. The addition of the organozincate of ethyl bromodifluoroacetate, prepared *in situ*, to a variety of benzotriazole-activated substituted *N*,*N*-dibenzyl imines **198**, afforded high yields of the $\beta^{3,2,2}$-amino acid esters **197** (*Scheme 57*).[32]

Michaut *et al.*[97] used an enantioselective (1,3) proton transfer to gain access to trifluoromethyl-β^3-amino acid **199**. A selection of trifluoroacetoacetate derived *N*-aryl imines **200**, were subjected to a $(DHQ)_2PHAL$ catalysed proton transfer. The resulting imines **201** were obtained in high yield with good enantioselectivity. The imines **201** were then hydrolysed to afford the trifluoromethyl-β^3-amino acid **199** in high yield (*Scheme 58*).[97]



R = Ph, 4-Pyr, 3-Pyr, heterocyclic, subst. aryl

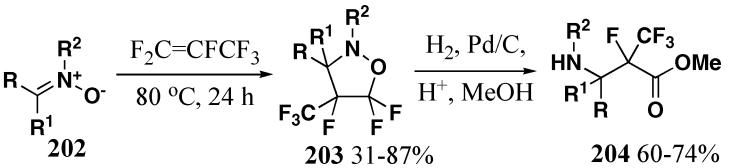
Scheme 57



Ar = Ph, 4-NO_2Ph, C_6F_5, Ph_2CH, 9-fluorenyl

Scheme 58

Jakoweicki *et al.*[98] demonstrated that nitrones **202** derived from a variety of aldehydes, undergo a 1,3-dipolar cycloaddition with fluorinated alkenes to produce isoxazolidines **203**. The isoxazolidines were then subjected to hydrogenolysis under acidic conditions to produce the highly fluorinated *N*-methyl $\beta^{3,2,2}$-amino esters **204** with mediocre diastereoselectivity (*Scheme 59*).[98]

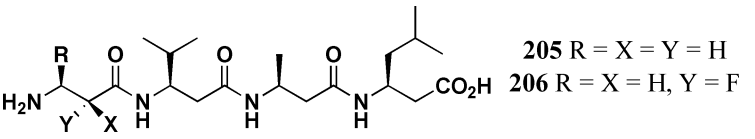


R = Ph, 4-MePh, 4-MeOPh, 2-thienyl, 3-Py, heteroaryl
R^1 = H, Ph
R^2 = Me, $(CH_2)_3OH$

Scheme 59

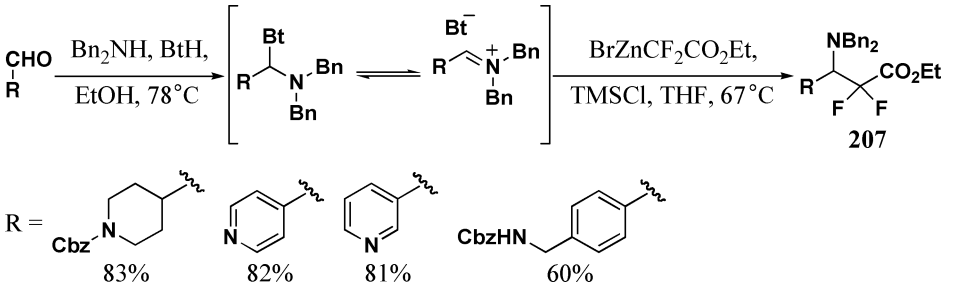
Hook *et al.*[99] discovered in their study that β-peptide **205**, which possesses an *N*-terminal β-homoglycine moiety, was stable to leucine aminopeptidase; the neighbouring β-amino acid residues apparently obstructing any potential hydrolysis. The β-peptide **206**, which has an *N*-terminal β^2-fluorohomoglycine residue also has the same properties (*Scheme 60*). As a result, peptide stability was not affected *via* the enhancement of electrophilicity of the terminal amide bond as well as without providing steric constraints by the fluoro substitution. Under the same pH conditions, both β-peptides were hydrolytically stable toward the exopeptidic activity of pronase.[99]

The replacement of hydrogen by fluorine induces modifications of chemical, physical, and biological properties of molecules. As a result, this leads to the generation of novel and potent biological, pharmacological, and chemotherapeutic agents. Recently, the area of fluorine-containing amino acids (FAAs) is expanding rapidly due to the benefits of



Scheme 60

fluorine substitution and the importance of amino acids in biochemical functions. FAAs are known to show antibacterial activity, to act as proteinase inhibitors, and to exhibit promising properties as candidates for peptide modification. Boyer and co-workers successfully synthesized $\beta^{2,2}$-difluoro-amino esters **207**, as potential basic metallocarbopeptidase inhibitors (*Scheme 61*).[32]

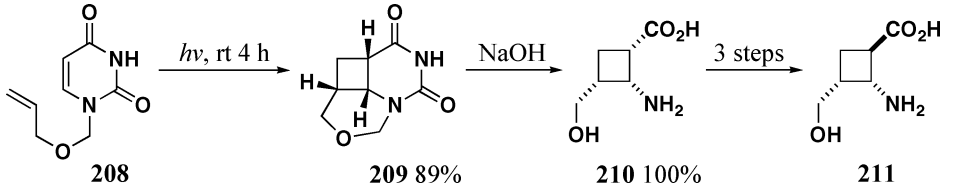


Scheme 61

2. Conformationally Constrained β-Amino Acids

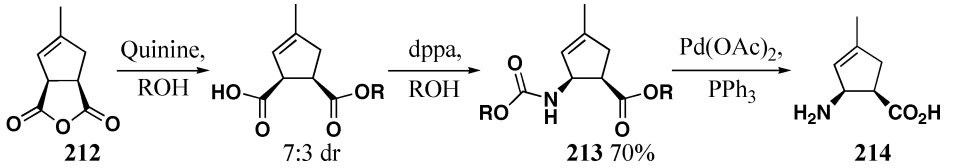
Given the recent development of applications for conformationally constrained β-amino acids, there has been an upsurge in the number of methods to access novel cyclic residues.[2,4–6]

Mondiere and co-workers[100] utilized a uracil tethered allyl ether **208** to perform a [2+2] photocycloaddition reaction to provide a single tricyclic adduct **209** in high yield. The resulting adduct was then subjected to hydrolysis to afford the all-*cis*-cyclobutane β-amino acid **210** bearing a 3-hydroxymethyl group in quantitative yield. The *diastereomeric*-cyclobutane β-amino acid **211** can be obtained by epimerisation of the carboxylic acid in three steps (*Scheme 62*).[100]



Scheme 62

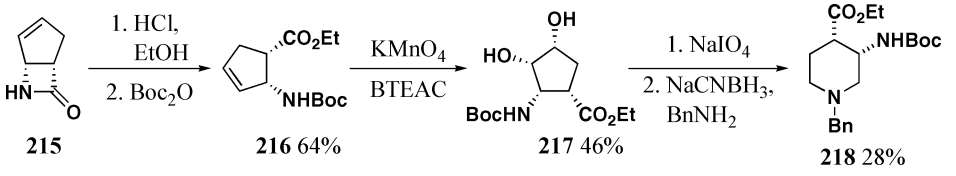
Hamersak and colleagues[101] accessed cyclopentane β-amino derivatives *via* a quinine-mediated kinetic resolution of a racemic anhydride **212**. A Curtius rearrangement followed and the *N*-carbamoyl β-amino ester **213** was obtained in high yield (*Scheme 63*). In order to



Scheme 63

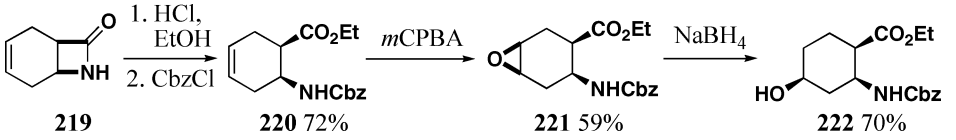
separate the *cis* and *trans* isomers, recrystallisation was required. Subsequent hydrogenolysis produced the *cis*- **214** and *trans*-β-amino methylenecyclopentane carboxylic acid.[101]

Kiss *et al.*[102] utilized a cyclopentenyl lactam **215** in the synthesis of conformationally constrained β-amino acids. The lactam **215** was hydrolysed to obtain the cyclopentenyl β-amino ester **216**. Subsequent dihydroxylation exclusively produced the *cis*-diol **217**. Oxidation of the diol, allowed for C-C bond cleavage to the bis-aldehyde, followed by reductive amination with benzyl amine and sodium cyanoborohydride to produce the piperidinyl β-amino ester **218**. This strategy allowed all four diastereoisomers of **218** to be produced (*Scheme 64*).[102]



Scheme 64

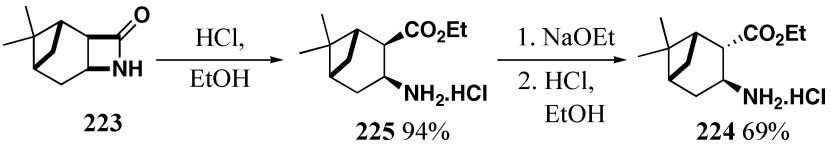
In an extension of their work, Kiss *et al.*[103] used a cyclohexenyl lactam **219** as a synthon to generate cyclohexyl β-amino esters **220**. The lactam **219** was easily hydrolysed to the cyclohexenyl β-amino ester **220**. On treatment with *m*-chloroperbenzoic acid the epoxide **221** was formed exclusively in the *cis*-configuration. The epoxide **221** was then regioselectively reductively cleaved using sodium borohydride to produce the 4-hydroxylated cyclohexyl β-amino ester **222** (*Scheme 65*).[103]



Scheme 65

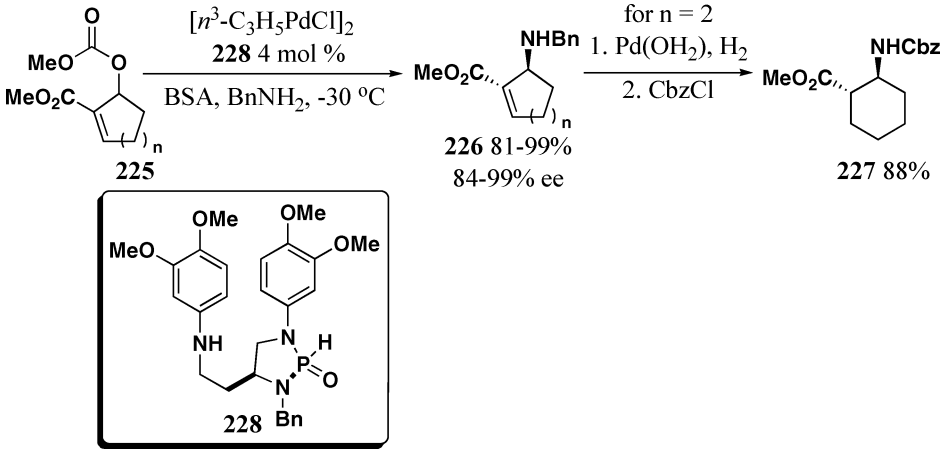
In a similar approach, Apopinene-derived monoterpene-fused β-lactams like **223** were utilized by Szakonyi *et al.*[104] to produce cyclic β-amino esters like **224**. The β-lactam was simply hydrolysed to produce the *cis*-β-amino ester **225**. All four diastereoisomers can be produced by this method also. The *trans*-β-amino ester **224** was produced by epimerisation of the *cis*-β-amino ester **225** (*Scheme 66*).[104]

Alternatively, Nemoto and co-workers produced cyclohexyl β-amino derivatives **225**, *via* Morita-Baylis-Hillman adducts, in a palladium catalysed allylic amination.[105]



Scheme 66

The aza-Morita-Baylis-Hillman products **226** were obtained with excellent enantioselectivity and in high yields. Subsequent hydrogenation produced the cyclohexane β-amino ester **227** with good diastereoselectivity (*Scheme 67*).[105]

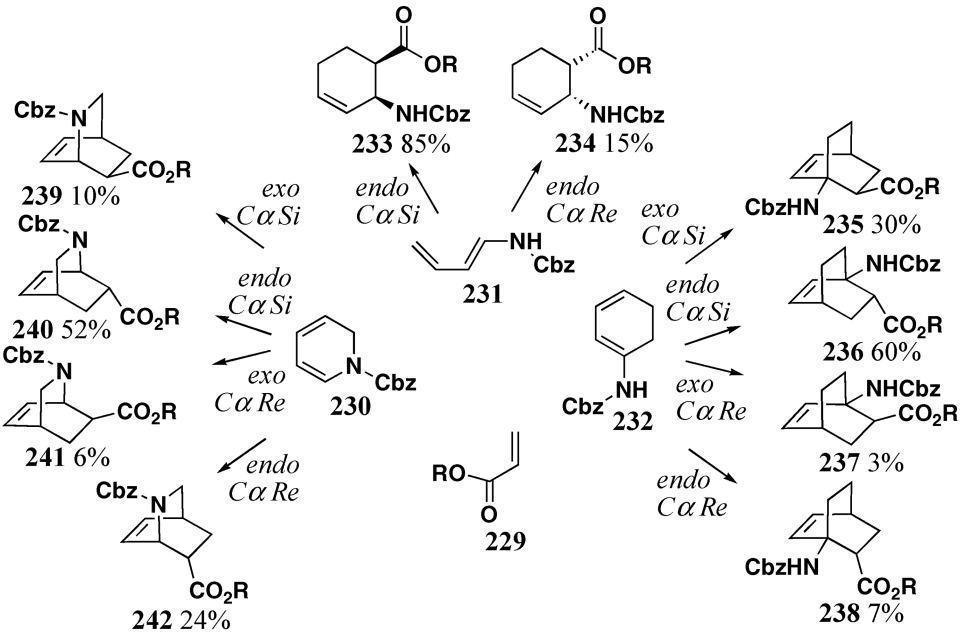


Scheme 67

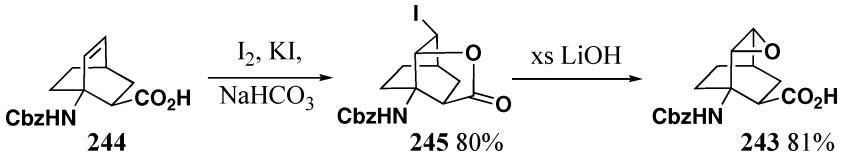
Songis *et al.*[106,107] have developed a number of methodologies for accessing norbornane β-amino acids. A Diels–Alder reaction was utilized, in both solution phase and on solid support, using (3*R*)-4,4-dimethyl-2-oxopyrrolidin-3-yl acrylate derivatives **229** and three *N*-Cbz-protected aminodienes **230**, **231** and **232**. The Diels-Alder cycloaddition of *N*-Cbz 1-aminobutadiene **231** with the acrylate **229** afforded the cyclic β-amino acids **233** and **234** with good *endo*-selective facial control. Similarly, the *N*-Cbz 1-aminocyclohexadiene **232** produced the bicyclic β-amino acids **235–238** with moderate *endo*-selectivity and good facial control. The reaction with *N*-Cbz-1,2-dihydropyridine **230** and the acrylates **229** proceeded with moderate *endo*-selectivity and poor facial selectivity to produce the cyclic β-amino acids **239–242** (*Scheme 68*).[106,107]

In an extension of this work Songis *et al.*[108] used an iodolactone approach to produce an oxiranyl norbornane β-amino acid **243**. The reaction of the unsaturated bicyclic β-amino acid **244** with iodine yielded the corresponding iodolactone **245** with excellent regio- and stereoselectivity. Subsequent treatment with excess lithium hydroxide afforded the bicyclic oxirane β-amino acid **243** in excellent yield (*Scheme 69*).[108]

Chola *et al.*[109] also used a similar Diels-Alder strategy to gain access to a 3,4,5,6-tetraacetoxycyclohexyl β-amino acid **246**. The precursor **247** was accessed *via* a Diels-Alder cycloaddition of furan **248** and maleic anhydride **249**, followed by a Curtius rearrangement. The resulting oxabicyclic adduct **247** was then ring opened by treatment with



Scheme 68



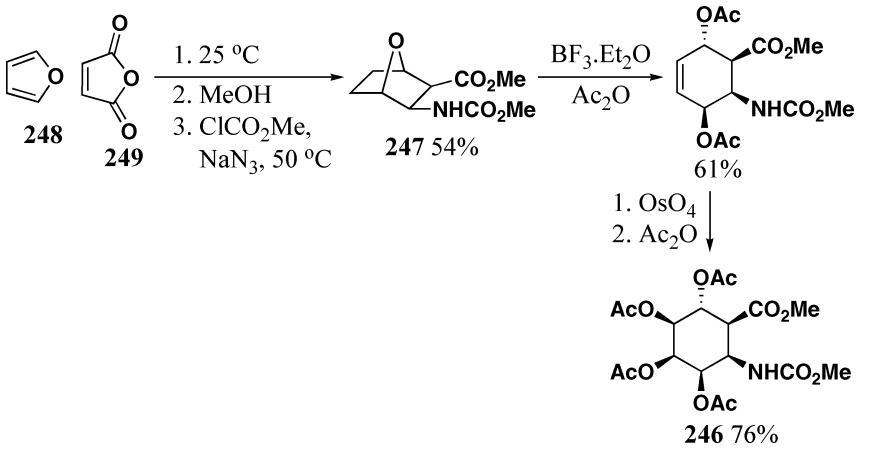
Scheme 69

a Lewis acid. An OsO_4-mediated dihydroxylation, followed by acylation gave the fully protected 3,4,5,6-tetrahydroxycyclohexyl β-amino ester **246** in good yield (*Scheme 70*).[109]

3. Glycoside Substituted β-Amino Acids

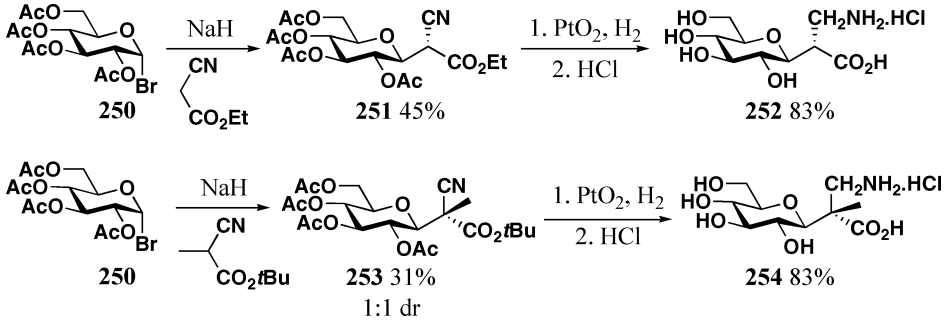
Given the special characteristics and properties of glycoside β-amino acids, syntheses of such residues are only now starting to appear in literature.

Inaba and co-workers produced a number of glycosyl β^2-amino acids starting from a glucose synthon.[110,111] The α-bromoglucose tetraacetate **250** was treated with sodium cyanoacetate prepared *in situ* to afford the glycoside **251** exclusively as the β-anomer. Subsequently, hydrogenation using platinum oxide reduces the nitrile to produce the protected glycosyl β^2-amino acid **252**. In an alternative pathway, α-bromo glucose tetraacetate **250**



Scheme 70

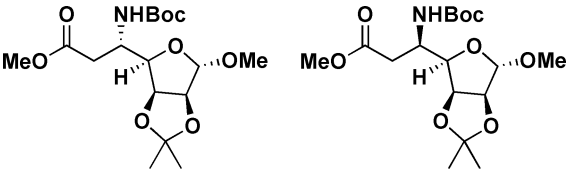
was treated with sodium 2-cyanopropionate to give a mixture of separable diastereoisomers **253** in low yield. The ensuing hydrogenation and hydrolysis produced the glycosyl $\beta^{2,2}$-amino acid **254** (*Scheme 71*).[110,111]



Scheme 71

The wide variety of biological activities of β-peptides such as resistance to enzyme degradation and enhancing protein binding ability have been areas of intense research activity. Extensive theoretical and molecular dynamics simulation studies have found that there is an intrinsic preference for the formation of 10–12-mixed helices in these peptides. Cationic β-peptides have been expected to apply as antibacterial agents through their direct action on the bacterial cell membrane and should be able to prevent rapid development of bacterial resistance. However, because of their inherent limited solubility in water, therapeutic applications of those β-peptides have hardly been investigated.

Sharma and co-workers[112] have successfully prepared new C-linked carbohydrate-β-amino acids (β-Caas) **255** and **256** as monomers in order to address the problems associated with water solubility and biological activity in β-peptides. Their studies have shown that there are no helical patterns observed in aqueous solutions for the peptides having bifunctional β-Caas after the removal of protecting groups. However, the 4 compounds **257**–**260** below were evaluated for their moderate antibacterial activity against a variety of bacterial



255 Boc-(*S*)-β-Caa-OMe **256** Boc-(*R*)-β-Caa-OMe

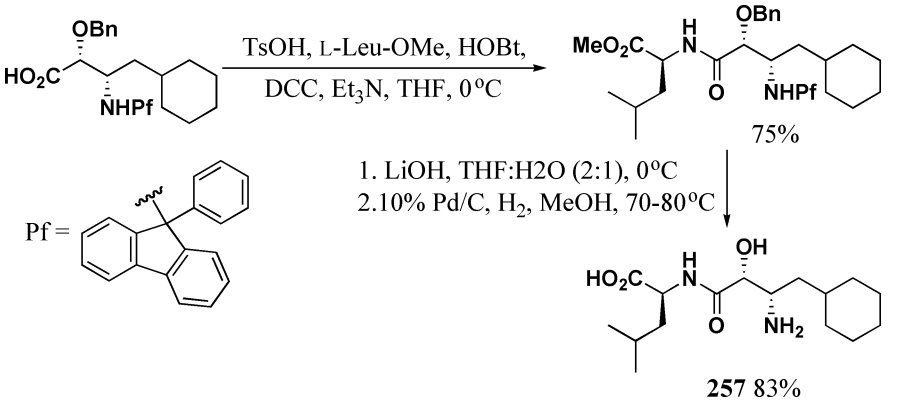
Scheme 72

strains (*Bacillus sphaericus*, *Bacillus subtilise*, *Serratia marcescens*, *Pseudomonas oleovorans*, *Klebsiella aerogenes* and *Chromobacterium violaceum*) through the measurement of the minimum inhibitory concentration (*Scheme 72*).

H-(*R*)-*β*-Caa-(NH_2)-(*S*)-*β*-Caa-(*R*)-*β*-Caa-OH.CF_3COOH **257**
H-(*S*)-*β*-Caa-(NH_2)-(*R*)-*β*-Caa-(*S*)-*β*-Caa-(*R*)-*β*-Caa-(NH_2)-(*S*)-*β*-Caa-(*R*)-*β*-Caa-OH.CF_3COOH **258**
H-(*R*)-*β*-Caa-(NH_2)-(*S*)-*β*-Caa-(*R*)-*β*-Caa-(*S*)-*β*-Caa-(NH_2)-OH.CF_3COOH **259**
H-(*R*)-*β*-Caa-(NH_2)-(*S*)-*β*-Caa-(*R*)-*β*-Caa-(*S*)-*β*-Caa-(NH_2)-(*R*)-*β*-Caa-(*S*)-*β*-Caa-OH.CF_3COOH **260**

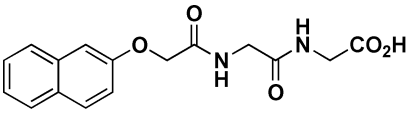
4. β-Amino Acid Applications

α-Hydroxy-*β*-amino acids are an important class of compounds due to their being constituents of many natural products such as paclitaxel, KRI 1230 and KRI 1314.[113] In recent years, both chemists and pharmacologists have paid considerable attention to application of *α*-hydroxy-*β*-amino acids protease inhibitors. Jang and co-workers[113] were able to successfully synthesize compound **257** and produced its dimer, which was expected to be a protease inhibitor (*Scheme 73*).

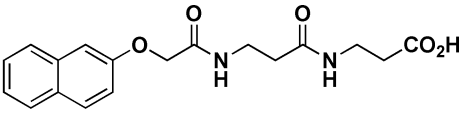


Scheme 73

Compounds **258** and **259** are *β*-amino acid derivatives, which form hydrogels by self-assembly. In a biological environment, this type of hydrogel has provided a new way to



258

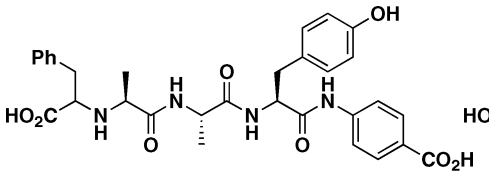


259

Scheme 74

improve stability and expand bioavailability in comparison with hydrogels formed from α-amino acid derivatives (*Scheme 74*).[114]

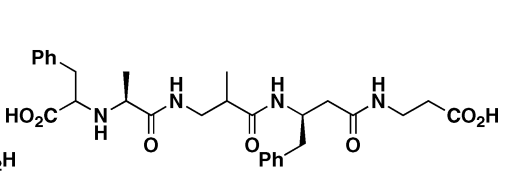
It is known that when an α-amino acid is replaced with the corresponding *C3*-β-amino acid at the scissile bond of a peptide, there will be a dramatic increase in the new, hybrid peptide's resistance to proteolysis while generally maintaining good to excellent target affinity.[115] Perlmutter and co-workers modified "CFP" (*N*-[1-(*R,S*)-carboxy-3-phenylpropyl]-Ala-Ala-Tyr-*p*-amino-benzoate) **260**, well known as an inhibitor of the metalloprotease EP24.15. It has been suggested that it is involved in the degradation of neuropeptides, hypothalamic regulation of pituitary function in the reproductive axis, in blood pressure regulation and in processing Aβ protein associated with Alzheimer's disease. The authors investigated the possibility of generating hybrid analogues of CFP which would be resistant to proteolysis by neprilysin, an enzyme related to EP24.15, and which readily cleaves CFP at the Ala-Tyr bond, but still has high affinity for EP 24.15.[115] They found that the best performing analogue **261** in the small library was the one bearing both a *rac*-C2β-Ala on the N-terminal side of the scissile bond, replacement of the C-terminal *p*-aminobenzoic acid with β-Gly and Phe replacing Tyr on the C-terminal side of the scissile bond (*Scheme 75*).[115]



CppN AN A~YN *p*-Ab

260

IC_{50} (24.15) 0.06 mM
(24.16) 0.12 mM
Degrdn by 24.11 100%



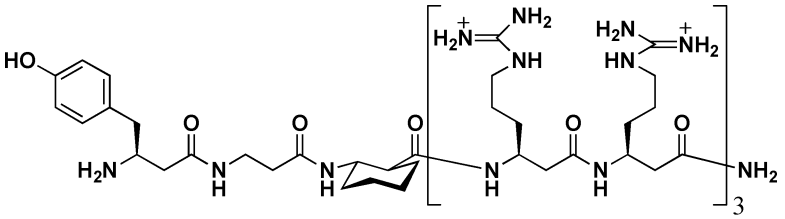
CppN AN A~FN G

261

IC_{50} (24.15) 2.8 mM
(24.16) 1.8 mM
Degrdn by 24.11 0%

Scheme 75

Akkarawongsa *et al.* reported three cationic β-peptides that can inhibit HSV-1 infection.[116] The most effective β-peptide is structure **262**. Although it did not inactivate virions in solution, induce cell resistance to infection or inhibit viral attachment to the cell receptor, it appeared to inhibit HSV-1 infection at a step between attachment and cell entry in cell culture at low micromolar concentrations (EC_{50} 3 μM). These findings constitute useful tools for extending the understanding of the processes of viral entry into cells and offer a new, potentially exciting, direction in antiviral drug development (*Scheme 76*).[116]



262

Scheme 76

IV. Conclusion

The broad range of techniques presented in this review covering a short period of time serves to emphasize the high level of research activity and creativity being brought by various researchers to the problem of access to substituted β-amino acids. At the start of this review a descriptor of different types of substituted β-amino acids was presented to aid the collection of related methods. The review has brought attention to the observation that most synthetic methods prepare β^3-amino acids. The methods for α-substituted or β^2-amino acids are in the minority. This of course represents a challenge to chemists that is beginning to be solved and accordingly in the next phase of research the scientific community can look forward to yet another collection of novel β-amino acid monomers for incorporation in libraries and use in applications.

Table of Abbreviations

AIBN	2,2′-Azo-*bis*-isobutyronitrile
βCaas	C-Linked carbohydrate β-amino acids
BINOL	1,1′-Bi-2-naphthol
BSA	Benzenesulfonic acid
BTEAC	Benzyltriethylammonium chloride
BtH	Benzotriazole
CAN	Ceric ammonium nitrate
CbzCl	Carbobenzyloxy chloride
CDI	Carbonyldiimidazole
Chx	Cyclohexyl
cod	1,5-Cyclooctadiene
CSA	Camphorsulfonic acid
dba	Dibenzalacetone
DCC	Dicyclohexylcarbodiimide
DIBAL	Diisobutyl aluminium hydride
DBU	8-Diazabicyclo[5.4.0]undec-7-ene
$(DHQ)_2PHAL$	Dihydroquinine-1,4-phthalazinediyl diether
DIB	(Diacetoxyiodo)benzene
DIC	Diisopropylcarbodiimide
DIEA	Diisopropylethylamine
DMAP	*N,N*-Dimethylaminopyridine

dppa	Diphenylphosphoryl azide
Fmoc	9-Fluorenylmethoxycarbonyl
Fmoc-OSu	9-Fluorenylmethoxycarbonyl O-succinimide ester
HMPA	Hexamethylphosphoramide
HOBt	Hydroxybenzotriazole
HSV-1	Herpes simplex virus type 1
KHMDS	Potassium *bis*(trimethylsilyl)amide
LAH	Lithium aluminium hydride
LDA	Lithium diisopropylamide
LiHMDS	Lithium *bis*(trimethylsilyl)amide
mCPBA	*meta*-Chloroperoxybenzoic acid
MoOPH	Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide) [MoO_5·Py·HMPA]
NFBS	*N*-Fluorobenzenesulfonimide
NaHMDS	Sodium *bis*(trimethylsilyl)amide
NMM	*N*-Methylmorpholine
PCC	Pyridinium chlorochromate
Pfp	Pentafluorophenyl
PMB	*para*-Methoxybenzyl
PMP	*para*-Methoxyphenyl
TBAF	*tetra*-Butylammonium fluoride
TBDMSCl	*tert*-Butyldimethylsilyl chloride
TBDPS	*tert*-Butyldiphenylsilyl
Tf	Trifluoromethanesulfonyl
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TMS	Trimethylsilyl
TPS	Triisopropylsilyl
Tr	Trityl (triphenylmethyl)
Ts	*para*-Toluenesulfonyl

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