Asymmetric Synthesis of α-Amino Carbonyls (Aldehydes, Ketones and Acids) using Lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide

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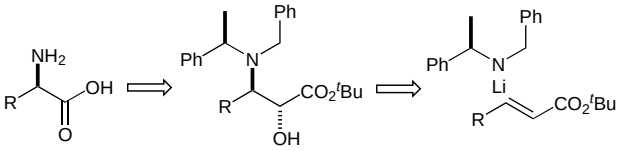
Abstract: The diastereoselective conjugate addition of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide to α,β-unsaturated esters and subsequent enolate hydroxylation, followed by reduction and oxidative cleavage provides a facile route to *N*,*N*-protected α-amino aldehydes and ketones. Further manipulation furnishes α-amino acids in high enantiomeric excess.

Key words: β-amino acids, conjugate addition, lithium amides, asymmetric synthesis, α-amino aldehyde, α-amino acid

α-Amino carbonyl compounds have been widely used as chiral synthons for natural product synthesis.[1] As a result of their synthetic utility, many efficient and versatile asymmetric syntheses of α-amino acids and derivatives have been investigated to allow for the incorporation of novel structural motifs not found within the chiral pool into these building blocks.[2] The most common route to the synthesis of α-amino aldehydes and ketones is that derived from their parent proteinogenic α-amino acids, typically via reduction to the amino alcohol and subsequent oxidation[3] or by application of Weinreb amide methodology.[4] The asymmetric synthesis of α-amino aldehydes and ketones has similarly been investigated, with these reactive functionalities having been prepared by nucleophilic additions to both protected imines[5] and pseudoephedrine *N*-Boc-α-amino acid amides,[6] as well as asymmetric alkylation of imines.[7] We have previously shown that the diastereoselective conjugate addition of lithium amides derived from α-methylbenzylamine to α,β-unsaturated esters provides an efficient route for the asymmetric synthesis of homochiral β-amino acid derivatives.[8] We report herein that lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide can be utilized for the asymmetric synthesis of *N*,*N*-protected α-amino aldehydes, *N*,*N*-protected α-amino ketones and α-amino acids from β-amino acid derivatives. While the Arndt–Eistert procedure provides a widely used route for the homologation of α-amino acids to β-amino acids,[9] the selective degradation of homochiral α-hydroxy β-amino esters is equally applicable as a route towards α-amino carbonyl derivatives (Figure).



Figure

We have previously demonstrated that *anti*-α-hydroxy-β-amino acids can be prepared by conjugate addition of a homochiral lithium amide with concomitant diastereoselective enolate oxidation with (–)-(camphorsulfonyl)oxaziridine.[10] Application of this methodology upon addition of lithium *(R)*-*N*-benzyl-*N*-α-methylbenzylamide to *tert*-butyl crotonate **1**, *tert*-butyl cinnamate **2** and *tert*-butyl 5-methyl-hex-2-enoate **3** gave the *anti*-α-hydroxy-β-amino esters **4**–**6**[11] with high diastereoselectivity (crude diastereomeric excess > 90% by ^{1}H NMR analysis) and as single diastereoisomers in excellent yield after purification. β-Amino esters **4**–**6** were subsequently reduced with $LiAlH_4$ to afford amino diols **7**–**9**[12] in uniformly excellent yield. H_5IO_6 mediated oxidation of amino diols **7**–**9** furnished the aldehydes **10**–**12**[13] in excellent yield, with no observable epimerisation (Scheme 1).

Having clearly demonstrated the utility of this methodology for the asymmetric synthesis of α-amino aldehydes, extension to the preparation of α-amino ketones was investigated. Thus, conjugate addition of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide to ethyl 1-cyclopentene-1-carboxylate **13** and subsequent enolate oxidation gave α-hydroxyl-β-amino ester **14** with high diastereoselectivity (crude diastereomeric excess > 90% by ^{1}H NMR analysis) and as a single diastereoisomer in 62% yield after purification. $LiAlH_4$ reduction to the amino diol **15** and subsequent oxidative cleavage furnished ketone **16**, although with slight (6%) epimerisation upon oxidation in this case (Scheme 2).

Having demonstrated the preparation of α-amino aldehydes and ketones, manipulation of α-amino aldehydes **10**–**12** to their α-amino acid hydrochloride salts was successfully accomplished in a two step procedure. Thus, sodium chlorite oxidation of aldehydes **10**–**12** gave the *N*-benzyl-*N*-α-methylbenzyl protected α-amino acid derivatives **17**–**19**[14] in 54–64% yield. Subsequent Pd-catalyzed hydride transfer deprotection and treatment with aqueous HCl gave (*R*)-alanine hydrochloride **20** and (*R*)-leucine hydrochloride **21**[15] in > 98% enantiomeric excess and (*R*)-

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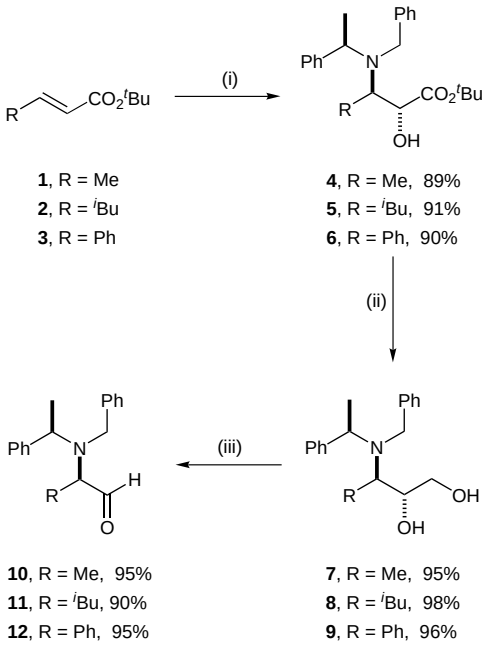
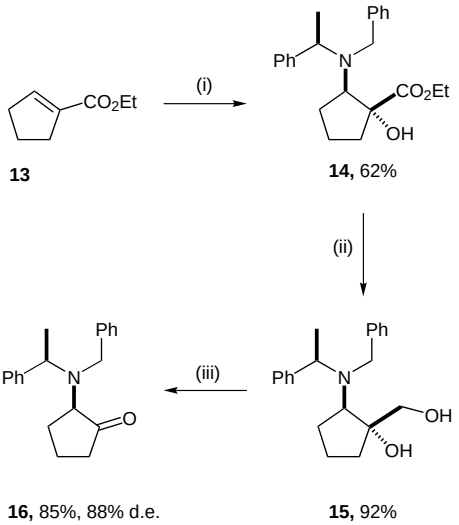


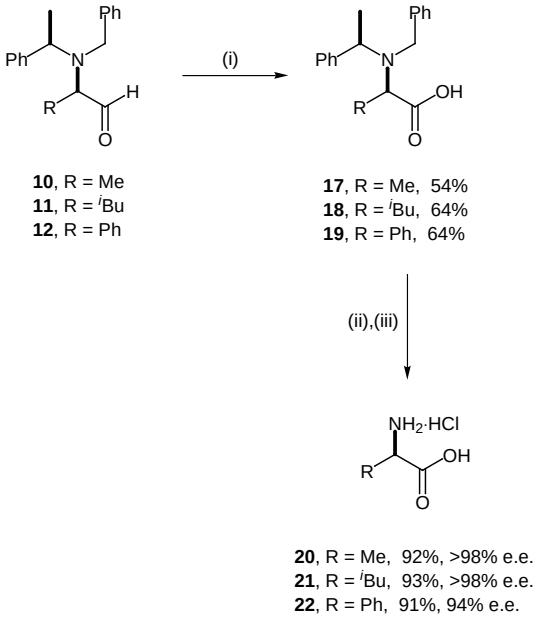
Scheme 1 *Reagents and Conditions:* (i). lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide (1.6 equiv), THF, –78 °C, 2 h then (–)-(camphorsulfonyl) oxaziridine, THF, –78 °C to r.t.; (ii). $LiAlH_4$, THF, –78 °C to r.t.; (iii). H_5IO_6, DCM–H_2O (1:1), 0 °C, 30 min.

phenylglycine hydrochloride **22** in 94% enantiomeric excess. The enantiomeric excesses of **20**–**22** were unambiguously determined in each case by ^1H NMR spectroscopic analysis of the corresponding Mosher's amide derivatives of the derived methyl esters and comparison to authentic racemic samples (Scheme 3).

In conclusion, this methodology represents a novel asymmetric synthesis of α-amino aldehydes, α-amino ketones and α-amino acids via the application of the highly diastereoselective conjugate addition of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide and concommitant enolate hydroxylation, reduction and oxidative cleavage. The extension of this protocol to the preparation of novel α-amino carbonyl derivatives is currently being investigated within our laboratory.



Scheme 2 *Reagents and Conditions:* (i). lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide (1.6 equiv), THF, –78 °C, 2 h then (–)-(camphorsulfonyl) oxaziridine, THF, –78 °C to r.t.; (ii). $LiAlH_4$, THF, –78 °C to r.t.; (iii). H_5IO_6, DCM–H_2O (1:1), 0 °C, 30 min.



Scheme 3 *Reagents and Conditions:* (i). $NaClO_2$, cyclohexene, MeOH, 0 °C; (ii). 4.4% HCO_2H, MeOH, Pd-C, 40 °C, 2 h; (iii). $HCl_{(aq)}$

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(11) All new compounds were fully characterized; experimental procedure for the synthesis of **5**; *n*-butyllithium (2.5 M, 6.2 mL, 15.5 mmol) was added dropwise to a stirred solution of *(R)*-*N*-benzyl-*N*-α-methylbenzylamine (3.4 g, 16.0 mmol) in THF (20 mL) at –78 °C under Ar. After 30 min, a solution of (*E*)-*tert*-butyl 5-methyl-hex-2-enoate **2** (1.84 g, 10.0 mmol) in THF (20 mL) was added via cannula. After 2 h, (–)-(camphorsulfonyl)oxaziridine (7.3 g, 32 mmol) was added at –78 °C and warmed to r.t. After 2 h, the reaction was cooled to –78 °C and quenched by the addition of saturated aq NH_4Cl (5 mL) and warmed to r.t. After concentration in vacuo, the residue was extracted with Et_2O, washed sequentially with 10% aq citric acid solution (20 mL), saturated aq bicarbonate solution (10 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography on silica gel (hexane–Et_2O, 10:1 to 5:1) gave **5** (2.54 g, 91%) as a colorless oil; $[\alpha]_D^{22}$ –18.9 (c 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 1722 (C=O); δ_H (500 MHz, $CDCl_3$) 7.48–7.22 (10 H, m, *Ph*), 4.35 (1 H, d, $J_{A,B}$ 15.6, NCH_A), 3.99 (1 H, d, $J_{2,3}$ 1.4, C(2)*H*), 3.95 (1 H, q, *J* 7.0, C(α)*H*), 3.66 (1 H, d, $J_{B,A}$ 15.6, NCH_B), 3.26 (1 H, m, C(3)*H*), 2.89 (1 H, br d, *J* 1.9, O*H*), 1.94, (1 H, m, C(5)*H*), 1.59 (2 H, m, C(4)H_2), 1.45 (9 H, s, (CH_3)$_3$C)), 1.29 (3 H, d, *J* 7.0, C(α)*Me*), 0.90 (3 H, d, *J* 6.8, C(5)CH_3), 0.68 (3 H, d, *J* 6.5, C(5)CH_3); δ_C (50 MHz, $CDCl_3$) 174.9 (*C*=O), 144.1, 143.5 (*Ph*$_{ipso}$), 128.4, 128.2, 127.9, 127.2, 126.5 (*Ph*$_{o-,m-,p-}$), 82.5 (*C*(CH$_3$), 71.1 (*C(2)*H), 59.4 (*C(a)*H), 57.0 (*C(3)*H), 51.0 (NCH_2), 36.9 (*C(4)*H$_2$), 28.0 (C(CH_3)$_3$), 24.1 (*C(5)*H), 23.6, 22.1 (C(5)(CH_3)$_2$), 20.4 (C(α)*Me*); HRMS (CI$^+$) $C_{26}H_{38}NO_3$ requires 412.2852; found 412.2856.
(12) Experimental procedure for the synthesis of **8**; $LiAlH_4$ (1 M in THF, 5.4 mL, 5.4 mmol) was added dropwise to a stirred solution of **5** (2.23 g, 5.4 mmol) in THF (10 mL) at –78 °C under N_2 and allowed to warm to r.t. After 24 h, 2 M $NaOH_{(aq)}$was added cautiously at 0 °C and the mixture heated at reflux for 30 min before being cooled, filtered through celite (eluent Et_2O), dried and concentrated in vacuo. Purification by column chromatography (Et_2O) gave **8** (1.81 g, 98%) as a colorless oil; $[\alpha]_D^{25}$ –21.0 (c 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 3401 (OH); δ_H (500 MHz, $CDCl_3$)7.47–7.26 (10 H, m, *Ph*), 4.06 (1 H, d, $J_{A,B}$ 14.6, NCH_A), 3.97 (1 H, q, *J* 6.9, C(α)*H*), 3.80 (1 H, d, $J_{B,A}$ 14.6, NCH_B), 3.57 (1 H, m, C(2)*H*), 3.41 (2 H, m, C(1)H_2), 2.90 (1 H, m, C(3)*H*), 2.75 (2 H, br s, CH(O*H*)CH$_2$O*H*), 1.90 (1 H, m, (C(5)*H*), 1.59 (1 H, m (C(4)H_A), 1.39 (3 H, d, *J* 6.9, C(α)*Me*), 1.36 (1 H, obscured, (C(4)H_B), 1.02 (3 H, d, *J* 6.6, C(5)CH_3), 0.87 (3 H, d, *J* 6.5, C(5)CH_3); δ_C (125 MHz, $CDCl_3$)144.0, 141.7 (*Ph*$_{ipso}$), 128.5, 127.9, 127.2, 126.9 (*Ph*$_{o-,m-,p-}$), 72.0 (*C(2)*H), 64.5 (*C(1)*H$_2$), 58.1 (*C(a)*H), 54.9 (*C(3)*H), 51.7 (NCH$_2$)37.9 (*C(4)*H$_2$), 25.2 (*C(5)*H), 23.3, 22.9 (C(5)(CH_3)$_2$), 16.3 (C(α)*Me*); HRMS (CI$^+$) $C_{22}H_{32}NO_2$ requires 342.2433; found 342.2436.
(13) Experimental procedure for the synthesis of **11**; H_5IO_6 (267 mg, 1.2 mmol) in H_2O (2 mL) was added to a stirred solution of the diol **8** (363 mg, 1.1 equiv) in DCM (2 mL) at 0 °C. After 30 min the mixture was extracted with Et_2O (2 × 20 mL) and the organic extracts washed with saturated sodium bicarbonate (20 mL) and brine (20 mL) to afford **11** (295 mg, 90%) as a colorless oil; $[\alpha]_D^{22}$+1.3 (c 0.63, $CHCl_3$); ν_{max}(film)/cm^{-1} 1723 (C=O); δ_H (500 MHz, $CDCl_3$) 9.42 (1 H, s, C*H*O), 7.51–7.27 (10 H, m, *Ph*), 4.16 (1 H, q, *J* 6.8, C(α)*H*), 4.00 (1 H, d, $J_{A,B}$ 14.7, NCH_A), 3.96 (1 H, d, $J_{B,A}$ 14.7, NCH_B), 3.41 (1 H, t, *J* 6.4, C(2)*H*CHO), 1.82 (1 H, app sept, *J* 6.6, C(4)*H*), 1.77 (1 H, m, C(3)H_2), 1.51 (3 H, d, *J* 6.9, C(α)*Me*), 1.50 (1 H, obscured, C(3)H_A), 0.95 (3 H, d, *J* 6.8, C(4)CH_3), 0.93 (3 H, d, *J* 6.8, C(4)CH_3); δ_C (125 MHz, $CDCl_3$) 203.9 (*C*=O), 144.2, 141.3, (*Ph*$_{ipso}$), 128.9, 128.8, 128.3, 127.8, 127.5 (*Ph*$_{o-,m-,p-}$), 64.2 (*C(a)*H), 58.9 (*C(2)*H), 51.1 (NCH$_2$), 36.1 *C(3)*H$_2$), 25.7 (*C(4)*H) 23.3, 23.2 (C(4)(CH_3)$_2$), 18.7 (C(α)*Me*); HRMS (CI$^+$) $C_{21}H_{28}NO$ requires 310.2171, found 310.2177.
(14) Experimental procedure for the synthesis of **18**; cyclohexene (1.0 mL) followed by $NaClO_2$ (95 mg, 1.05 mmol) was added to a stirred solution of the aldehyde **11** (295 mg, 0.96 mmol) in MeOH (5 mL) at 0 °C. After 30 min, the mixture was extracted with Et_2O (2 × 20 mL) and the organic extracts washed with saturated sodium bicarbonate (20 mL) and brine (20 mL) before concentration in vacuo to afford **18** (198 mg, 64%) as a colorless oil; $[\alpha]_D^{25}$+28.9 (c 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 1704 (C=O); δ_H (500 MHz)7.56–7.30 (10 H, m, *Ph*), 4.17 (1 H, q, *J* 6.8, C(α)*H*), 4.05 (1 H, d, $J_{A,B}$ 15.1, NCH_A), 3.99 (1 H, d, $J_{B,A}$ 15.1, NCH_B), 3.50 (1 H, dd, $J_{2,3A}$ 7.6, $J_{2,3B}$ 6.9, C(3)*H*), 2.00 (1 H, app sept, *J* 6.7, (C(4)*H*), 1.76 (1 H, m, C(4)*H*), 1.58 (2 H, m, C(3)H_2), 1.41 (3 H, d, *J* 6.8, C(α)*Me*), 0.92 (3 H, d, *J* 6.7, C(4)CH_3), 0.88 (3 H, d, *J* 6.7, C(4)CH_3); δ_C (62.5 MHz, $CDCl_3$) 178.3 (*C*=O), 143.3, 140.6, (*Ph*$_{ipso}$), 129.4, 129.1, 129.0, 128.6, 128.2, 128.0, 127.6 (*Ph*$_{o-,m-,p-}$), 59.9, 59.3 (*C(a)*H, *C(2)*H), 52.1 (NCH$_2$)39.4 (*C(3)*H$_2$), 26.0 (*C(4)*H), 22.8 (C(4)(CH_3)$_2$), 18.7 (C(α)*Me*); HRMS (CI$^+$) $C_{21}H_{28}NO_2$ requires 326.2120; found 326.2123.
(15) Experimental procedure for the synthesis of **21**; Pd-C (77 mg, 10 mol%) was added to a stirred solution of **18** (77 mg, 0.24 mmol) in 4.4% formic acid in MeOH (10 mL) and heated at 40 °C for 2 h. Upon cooling, the suspension was filtered through celite®, acidified (1 mL, 10 M HCl) and concentrated in vacuo to afford **21** (37 mg, 93%) as a white solid; $[\alpha]_D^{25}$ –3.2 (c 0.5, H_2O); Lit.[16](*ent)*$[\alpha]_D^{20}$+2.8 (c 0.61, H_2O); δ_H (500 MHz, D_2O) 3.97 (1 H, m, CH_2CHCO_2H), 1.75 (1 H, app. quintet, *J* 5.9, $(CH_3)_2CHCH_2$), 1.64 (2 H, m, $CHCH_2CH$), 0.87 (3 H, d, *J* 6.2, $(CH_3)_2CH$), 0.85 (3 H, d, *J* 6.2, $(CH_3)_2CH$); the ee was determined to be > 98% through derivatization of the methyl ester as its Mosher's amide.
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