Lithium (α-Methylbenzyl)allylamide: A Differentially Protected Chiral Ammonia Equivalent for the Asymmetric Synthesis of β-Amino Acids and β-Lactams

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The addition products from the highly stereoselective conjugate additions of lithium (α*S*)-(α-methylbenzyl)allylamide to α,β-unsaturated *tert*-butyl esters are efficiently deallylated with tris(triphenylphosphine)rhodium(I) chloride and converted, after transesterification to the methyl esters and cyclisation with methylmagnesium bromide, to the corresponding homochiral *N*-(α-methylbenzyl)-4-substituted-azetidin-2-ones.

The increasing number of known naturally occurring and synthetic pharmacologically important β-amino acids and derived β-lactams has stimulated many investigations into their asymmetric synthesis.[1] One of the more attractive methods for their asymmetric synthesis involves the stereoselective Michael addition of a homochiral ammonia equivalent to an α,β-unsaturated ester.[2–4] We have previously demonstrated that lithium (α-methylbenzyl)benzylamide **1** is an extremely useful chiral ammonia equivalent for the asymmetric synthesis of β-amino acids and derivatives [*e.g.* the synthesis of (3*R*)-(−)-3-aminobutanoic acid **2** in Scheme 1].[4] Amide **1** is particularly attractive because it is readily available and inexpensive, its Michael addition reactions are highly stereoselective and the two *N*-benzyl groups are readily removable by hydrogenolysis.[4–6]

The major limitations of the chiral ammonia equivalent **1** manifest themselves in the final deprotection step. Both protecting groups are removed by hydrogenolysis and this is incompatible with a number of essential functional groups such as alkenes. Furthermore, for the asymmetric synthesis of β-lactams, differential deprotection of the two NH bonds is desirable so that an *N*-protected β-lactam can be formed directly. While we[7] and others[8] have observed that in some cases it is possible to control the hydrogenolysis deprotection such that selective removal of the *N*-benzyl group in preference to the *N*-(α-methylbenzyl) group can be achieved, this is generally not a satisfactory procedure and does not avoid the incompatibility problems. We describe herein the use of lithium (α-methylbenzyl)allylamide **3** as a differentially protected chiral ammonia equivalent for the asymmetric synthesis of protected β-amino acids and β-lactams.

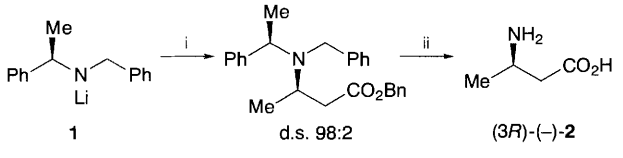
Our previous molecular modelling studies[9] into the origins of the highly stereoselective conjugate addition reactions of lithium (α-methylbenzyl)benzylamide **1** suggested that the same control elements should still be operative in the case of lithium (α-methylbenzyl)allylamide **3**. Homochiral (α*S*)-α-methylbenzylamine was treated with butyllithium followed by allyl bromide to generate, after column chromatography and distillation, (α*S*)-(α-methylbenzyl)allylamine in 65% yield {$[\alpha]_D^{21}$ −63.2 (*c* 1.36, $CHCl_3$)}.

Treatment of (α*S*)-(α-methylbenzyl)allylamine in THF at −78 °C with butyllithium (0.8 equiv.) generated a solution of lithium (α*S*)-(α-methylbenzyl)allylamide **3** to which was added *tert*-butyl crotonate. Standard work-up generated (3*S*,α*S*)-**4** as a single diastereoisomer (Scheme 2). Deallylation was achieved cleanly and efficiently by treatment of (3*S*,α*S*)-**4** with tris-(triphenylphosphine)rhodium(I) chloride in acetonitrile–water[10] to generate (3*S*,α*S*)-**5**. Hydrogenolysis of the *N*-α-methylbenzyl group, acid hydrolysis of the *tert*-butyl ester and ion exchange chromatography (Scheme 2) released (3*S*)-(+)-3-aminobutanoic acid, (3*S*)-**2** {$[\alpha]_D^{21}$ +39.2 (*c* 0.48, H_2O); lit.,[11] $[\alpha]_D^{18}$ +38.8 (*c* 0.48, H_2O)}. Correlation of the sign of the specific rotation of (3*S*)-**2** with the known values for (3*S*)-(+)- and (3*R*)-(−)-3-aminobutanoic acid established the absolute configuration of the sample prepared as above. Hence the sense of addition of the lithium amides **1** and **3** to *tert*-butyl crotonate are the same as expected from the modelling studies.

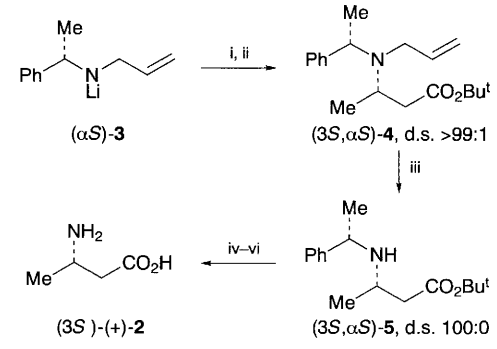
Transesterification of the *tert*-butyl ester (3*S*,α*S*)-**5** to the methyl ester (3*S*,α*S*)-**6** was readily achieved with a saturated solution of HCl-(g) in methanol (Scheme 3). Addition of methylmagnesium bromide to a solution of (3*S*,α*S*)-**6** in diethyl ether at 0 °C followed by quenching with pH 7 buffer generated the β-lactam (4*S*,α*S*)-1-(α-methylbenzyl)-4-methylazetidin-2-one, (4*S*,α*S*)-**7**.

This methodology appears to be general for the asymmetric synthesis of *N*-protected 4-substituted azetidin-2-ones as shown in Table 1. Of particular importance is its applicability to the synthesis of (4*R*,α*S*)-1-(α-methylbenzyl)-4-propenylazetidin-2-one, inaccessible *via* previous methodologies yet the type of substituent required for the asymmetric synthesis of, for example, thienamycin.[6,12]

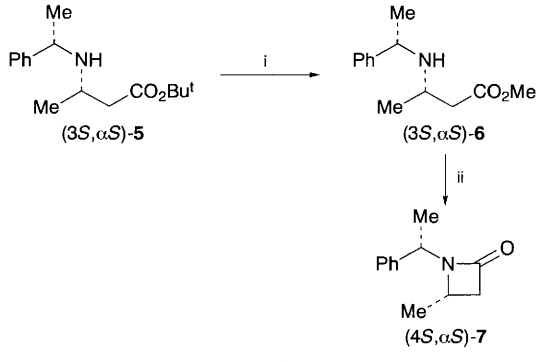
In conclusion, we have demonstrated that lithium (α-methylbenzyl)allylamide **3** is an efficient and versatile differentially protected ammonia equivalent for the asymmetric



Scheme 1 *Reagents and conditions*: i, MeC(H)=C(H)CO_2Bn, 85%; ii, Pd/C/H_2, 100%

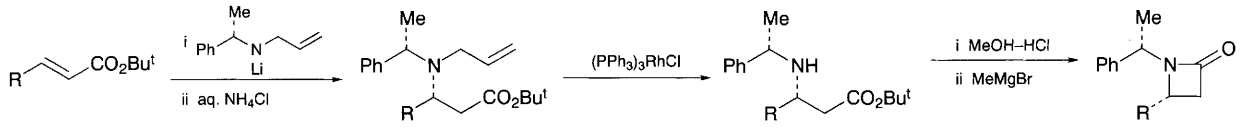


Scheme 2 *Reagents and conditions*: i, MeC(H)=C(H)CO_2Bu^t; ii, aq. NH_4Cl, 92%; iii, [$(PPh_3)_3RhCl$], 96%; iv, Pd$(OH)_2$/C/H_2; v, H^+; vi, ion exchange, 90%



Scheme 3 *Reagents and conditions*: i, MeOH–HCl, 100%; ii, MeMgBr, 77%

Table 1 Asymmetric synthesis of *N*-protected 4-substituted azetidin-2-ones



R	Yield (%)	d.s.[a]	**8** $[\alpha]_D^{21}$ ($CHCl_3$)	Yield (%)	d.s.[b]	**9** $[\alpha]_D^{21}$ ($CHCl_3$)	Yield (%)	d.s.	**10** $[\alpha]_D^{21}$ ($CHCl_3$)
Me	92	>99:1	+16.9 (*c* 1.80)	96	100:0	−36.3 (*c* 1.78)	77	100:0	−68.9 (*c* 1.61)
Et	85	>99:1	+18.5 (*c* 1.88)	92	100:0	−54.0 (*c* 1.81)	74	100:0	−8.9 (*c* 1.84)
Pr^i	88	>99:1	+52.7 (*c* 1.85)	95	100:0	−52.7 (*c* 1.57)	76	100:0	+26.1 (*c* 1.96)
Ph	97	>99:1	−2.1 (*c* 3.24)	95	100:0	−16.3 (*c* 1.45)	78	100:0	+57.9 (*c* 1.06)
2-furyl	97	>99:1	[c]	80	100:0	−1.5 (*c* 1.74)	82	100:0	+36.7 (*c* 1.96)
(E)-MeCH=CH	78	>98:2	+2.7 (*c* 1.67)	92	100:0	−45.1 (*c* 1.69)	78	100:0	−39.4 (*c* 1.02)

[a]The d.s. is measured by 500 MHz ^1H NMR analysis. >99:1 means 0.5 ± 0.5% of the minor diastereoisomer is observed. [b] Crude d.s. corresponds to that for **8**, but the minor diastereoisomer is more polar and disappears on column chromatography. [c] This adduct spontaneously undergoes an intramolecular Diels–Alder reaction and hence no meaningful optical rotation could be recorded. Competition between the Diels–Alder reaction and the deprotection explains the somewhat lower yield in the deallylation step.

synthesis of β-amino acid and β-lactam derivatives *via* a conjugate addition strategy.

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