Discussion Addendum for:
Lithium Amides as Homochiral Ammonia Equivalents for Conjugate Additions to α,β-Unsaturated Esters: Asymmetric Synthesis of (S)-β-Leucine

Stephen G. Davies,¹ Ai M. Fletcher, Paul M. Roberts, and James E. Thomson

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, OX1 3TA, U.K.


The conjugate addition of enantiopure lithium N-benzyl-N-(α-methylbenzyl)amide to α,β-unsaturated esters and amides displays high diastereoselectivity with extremely wide substrate scope and thus this process has been recognized as one of the most robust and reliable
methods to prepare β-amino acid derivatives. The stereochemical outcome of this process is predictable in most cases and is rationalised by a transition state mnemonic. This methodology has found numerous applications, including in the areas of target synthesis and molecular recognition phenomena, and was comprehensively reviewed in 2005, 2012, and 2017.

Lithium Amide Family and Selective Deprotection Strategies

In addition to the most commonly employed lithium amide reagent, lithium N-benzyl-N-(α-methylbenzyl)amide, more than 20 analogues which incorporate allyl, various substituted benzyl, haloalkyl, and methylheteroaryl groups have been developed for conjugate addition. Enantiomerically pure lithium amides 18 and 21 as a chiral “hydroxylamine equivalent” and a chiral “aniline equivalent”, respectively, have also been developed. Conjugate additions of some representative members of the lithium amide family are presented below and the conjugate addition products 7, 10, 13, 16, 19 and 22 were isolated as single diastereoisomers (Scheme 1).
Several chemoselective deprotection methods for removal of the N-protecting groups have been developed. For example, treatment of 23 with ceric ammonium nitrate (CAN) in MeCN/H₂O at rt for 2 h¹² gave selectively mono-debenzylated β-amino ester 24 in 60% yield.¹³ Oxidative removal of the N-3,4-dimethoxybenzyl group within 25 with 2,3-
dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave 26 in 98% yield. The \( p \)-methoxy variant, incorporating an \( N \)-alpha-methyl-\( p \)-methoxybenzyl group, can be removed under various acidic conditions; for example: treatment of 10 with \( \text{HCO}_2\text{H} \) and \( \text{Et}_3\text{SiH} \) gave 27 in 81% yield.\(^7\) Treatment of 28 with a Pd catalyst and \( N,N \)-dimethylbarbituric acid 29 smoothly removed the \( N \)-allyl group to give 30 in 97% yield (Scheme 2).\(^{15}\)

Scheme 2. Representative chemoselective \( N \)-deprotections [PMP = 4-methoxyphenyl; TDBMS = tert-butyldimethylsilyl]

\[ \text{Scheme 2. Representative chemoselective } N \text{-deprotections [PMP = 4-methoxyphenyl; TDBMS = tert-butyldimethylsilyl]} \]

**\( \alpha \)-Functionalisation of \( \beta \)-Amino Acid Derivatives**

In order to expand the structural diversity of the accessible \( \beta \)-amino acid derivatives, \( \alpha \)-functionalisation of the \( \beta \)-amino ester has been investigated. \( \alpha \)-Functionalisation of the \( \beta \)-amino acid derivatives can be achieved via elaboration of the intermediate enolate resulting from
conjugate addition of a lithium amide reagent to an $\alpha,\beta$-unsaturated ester with an electrophile (tandem manner). Alternatively, $\alpha$-functionalisation can be achieved upon formation of the corresponding $\beta$-amino enolate upon deprotonation of a $\beta$-amino ester with a strong base (e.g., LDA, NaHMDS etc) followed by treatment with an electrophile (stepwise manner). The stereochemical outcome and diastereoselectivity of these processes depends on the nature of the substrate and the electrophile.\(^{16}\)

For example, “tandem” conjugate addition/alkylation upon reaction of (S)-32 and $\alpha,\beta$-unsaturated ester 31 followed by the addition of allyl bromide to the intermediate lithium (Z)-$\beta$-amino enolate (Z)-33 gave 34 in 60% yield as an 85:15 mixture of C(2)-epimers,\(^{17}\) while treatment of $\beta$-amino ester 35 with LiTMP to form the corresponding enolate (E)-36 in situ and addition of acrolein 37 gave 38 in 96% yield as a single diastereoisomeric product (Scheme 3).\(^{18}\)

**Scheme 3. “Tandem” and “stepwise” $\alpha$-functionalisation strategies**

Treatment of $\beta$-amino enolates, derived from the conjugate addition of an enantiopure lithium amide 40 to an $\alpha,\beta$-unsaturated ester 39, with various electrophiles facilitated the preparation of a range of $\alpha$-fluoro, $\alpha$-mercapto, and $\alpha$-hydroxy-$\beta$-amino acid derivatives 41. For example, Duggan and co-workers reported the tandem conjugate addition/fluorination of $\alpha,\beta$-unsaturated ester using the electrophilic fluorinating agent $N$-fluorobenzenesulfonylimide (NFSI), which gave anti-$\alpha$-fluoro-$\beta$-amino ester 42 in 77% yield.\(^{19}\) Similarly, anti-$\alpha$-tart-butylthio-$\beta$-amino ester 43 was obtained in 88% yield as a single diastereoisomer by in situ enolate trapping with TsS$^\text{Bu}$.\(^{20}\) In situ enolate oxidation with
the requisite antipode of camphorsulfonyloxaziridine (CSO) has been well-established as a powerful tool for asymmetric anti-aminohydroxylation and has been frequently reported in the literature (>50 examples in the last 5 years). For example, 44 was obtained by conjugate addition of (R)-32 to the requisite α,β-unsaturated ester followed by enolate oxidation with (–)-CSO in 80% yield as a single diastereoisomer (Scheme 4).21,22

![Scheme 4](image)

**Scheme 4. α-Functionalisation of β-amino enolates**

The corresponding syn-α-hydroxy-β-amino ester 47 can be prepared via an oxidation/diastereoselective reduction protocol.23 For example, Swern oxidation of anti-α-hydroxy-β-amino ester 45 gives the corresponding ketone 46, and reduction with either NaBH₄ in MeOH or DIBAL-H in THF gives typically a >90:10 mixture of syn-47 and anti-45, respectively, and the corresponding syn-α-hydroxy-β-amino ester 47 can be isolated as a single diastereoisomer. Representative recent examples are shown below (Scheme 5).22,24,25
Scheme 5. Preparation of syn-β-amino-α-hydroxy esters

Cyclic β-Amino Acid Syntheses

Preparations of enantiopure cyclic β-amino acids were also developed via conjugate addition of lithium N-allyl-N-(α-methylbenzyl)amide or lithium N-but-3-enyl-N-(α-methylbenzyl)amide to a suitable α,β-unsaturated ester followed by ring-closing metathesis as the key steps. For example, conjugate addition of lithium (S)-N-allyl-N-(α-methylbenzyl)amide (S)-6 to α,β-unsaturated ester 51 (derived from sorbic acid) gave β-amino ester 52 in 78% yield. Ring-closing metathesis of 52 with Grubbs I catalyst gave the cyclic β-amino ester 53 in 77% yield. Stepwise hydrogenation of 53 in the presence of Wilkinson’s catalyst and subsequent hydrogenolytic removal of the N-protecting group gave amino ester 55 in 79% yield (from 53). Acid-mediated ester hydrolysis gave (S)-homoproline 56 in 96% yield (Scheme 6). Application of this methodology, involving the conjugate addition of an enantiopure lithium amide incorporating alkenyl functionality to the requisite α,β-unsaturated esters followed by ring-closing metathesis, provided key intermediates for a wide range of azacyclic scaffolds such as cyclic β-amino acids 57–59, pyrrolidines,27 piperidines,28–30 and pyrrolizidines.17,31,32
Scheme 6. Preparation of cyclic β-amino acids

Rearrangement towards α-Amino Acids

Synthetic routes to access natural and non-natural α-amino acid derivatives have also been developed via the aminohydroxylation of an α,β-unsaturated ester and stereospecific rearrangement via the corresponding aziridinium ion intermediate. For example, aminohydroxylation of 1 with (R)-32 and (−)-CSO gave anti-α-hydroxy-β-amino ester 60 in 56% yield and >99:1 dr. Treatment of 60 with Tf₂O and DTBMP 61 activates the hydroxy group within 60 as a triflate followed by formation of the corresponding aziridinium ion intermediate 62 upon displacement by the adjacent tertiary amino group. Subsequent regioselective ring-opening of 62 with H₂O gave β-hydroxy-α-amino ester 63 in 68% yield and >99:1 dr after purification. Deprotection of 63 via hydrogenolysis in the presence of a Pd catalyst followed by acid-mediated hydrolysis gave (S,S)-β-hydroxyleucine 64 in 69% yield and ≥96:4 dr over 2 steps (Scheme 7). This rearrangement progresses via an aziridinium ion intermediate using other nucleophiles (such as fluoride and azide) allowed access to various β-functionalized α-amino acid derivatives in high diastereoisomeric purity.
In conclusion, the conjugate addition of enantiopure lithium amides to α,β-unsaturated carbonyl compounds has consistently been demonstrated in high chemical yield and excellent diastereoselectivity with a wide range of substrate scope. Significant development for the elaboration of the resultant β-amino ester products or β-amino enolates has been achieved in the past few years and this will continuously contribute not only to the area of amino acid/peptide chemistry but also in the areas of natural products and pharmaceutically important target syntheses.

References

1. Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, OX1 3TA, U.K. E-mail: steve.davies@chem.ox.ac.uk


Steve Davies is the fifth Waynflete Professor of Chemistry at the University of Oxford. He has been the recipient of numerous prizes, including the following Royal Society of Chemistry awards: Hickinbottom Fellowship, Corday Morgan Medal and Prize, Award for Organometallic Chemistry, Bader Award, Tilden Lectureship, Award for Stereochemistry, and Perkin Prize for Organic Chemistry. He has published more than 600 papers and has research interests ranging from organometallic chemistry, asymmetric synthesis and natural product chemistry to medicinal chemistry and drug discovery. In 2014, he was elected Dr Honoris Causa, University of Salamanca (Spain).

Ai Fletcher obtained a B. Eng. from Keio University, Japan, then moved to the U.K. where she pursued a Ph.D. at Imperial College London under supervision of Professor Chris Braddock. Since completing her Ph.D. in 2004, she has explored a range of chemistry as a post-doctoral researcher at the University of Regensburg (Professor Oliver Reiser), and at the University of Bath (Professor Michael Willis), she joined the group of Professor Steve Davies in Oxford in 2007, where she has been involved with the development of asymmetric synthetic methodology and its application to the total synthesis of natural products.

Paul Roberts graduated with an M.Chem. from Jesus College, Oxford, in 2000, which was followed by a D.Phil. with Professor Steve Davies in the area of the asymmetric synthesis of piperidine alkaloids employing a ring closing metathesis approach. In 2005, he took up a post-doctoral position with Professor Davies at Oxford, where his research interests centre upon natural product synthesis and the development of new stereoselective methodologies, for example to effect the chemo- and stereoselective functionalisation of allylic amines with a range of electrophilic reagents.
Jim Thomson studied chemistry at the University of Oxford where he gained an M.Chem. (2003) and then D.Phil. (2007), working with Professor Steve Davies in the area of β-amino acid organocatalysis. He then took up a post-doctoral position with Professor Davies, as a Junior Research Fellow, and in 2010 was appointed to a Research Fellowship in association with St. Catherine’s College, Oxford. His research interests centre upon the development of novel asymmetric transformations and the total synthesis of natural products.