Organic Syntheses

Discussion Addendum for:

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

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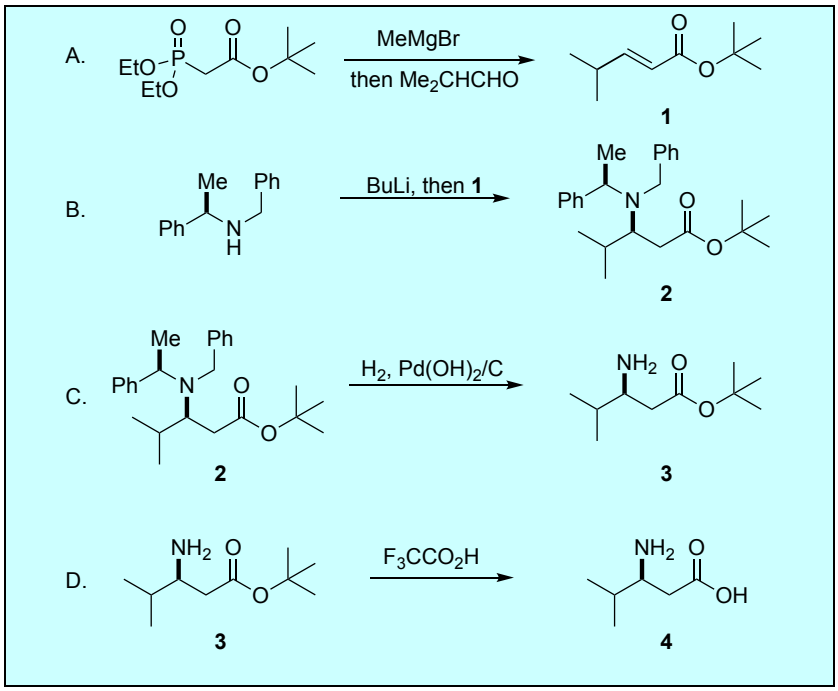

The conjugate addition of enantiopure lithium *N*-benzyl-*N*-(α-methylbenzyl)amide to α,β-unsaturated esters and amides displays high diastereoselectivity with extremely wide substrate scope and thus this process has been recognized as one of the most robust and reliable

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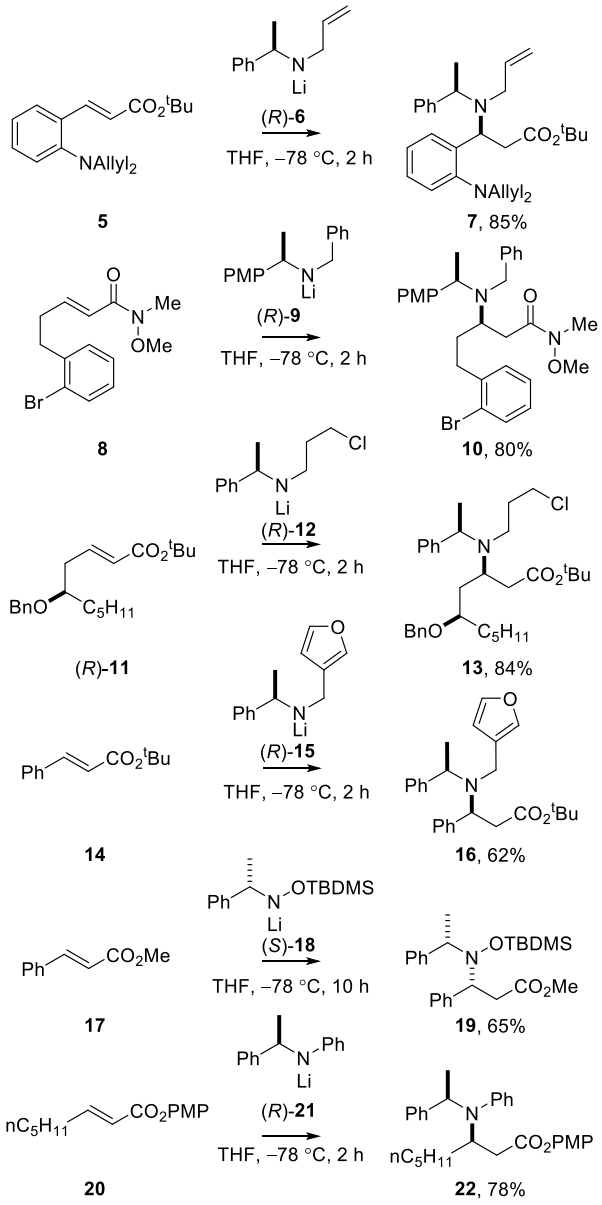
methods to prepare β-amino acid derivatives. The stereochemical outcome of this process is predictable in most cases and is rationalised by a transition state mnemonic.[2] This methodology has found numerous applications, including in the areas of target synthesis and molecular recognition phenomena, and was comprehensively reviewed in 2005,[3] 2012,[4] and 2017.[5]

Lithium Amide Family and Selective Deprotection Strategies

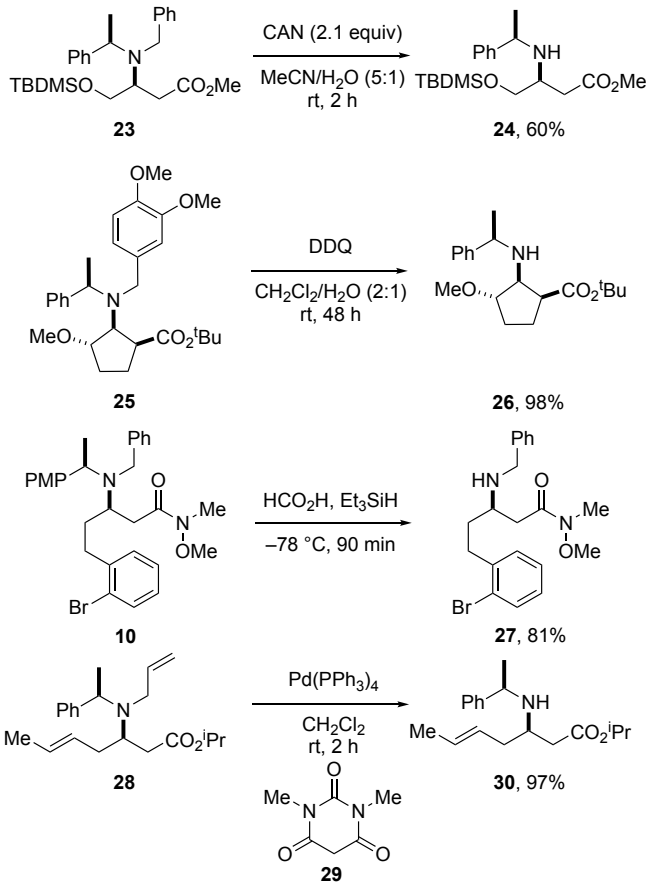
In addition to the most commonly employed lithium amide reagent, lithium *N*-benzyl-*N*-(α-methylbenzyl)amide, more than 20 analogues which incorporate allyl, various substituted benzyl, haloalkyl, and methylheteroaryl groups have been developed for conjugate addition. Enantiomerically pure lithium amides **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).



Scheme 1. Conjugate additions of representative lithium amides [PMP = 4-methoxyphenyl; TDBMS = *tert*-butyldimethylsilyl][6-11]

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/H_2O at rt for 2 h[12] 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.[14] The *p*-methoxy variant, incorporating an *N*-α-methyl-*p*-methoxybenyl group, can be removed under various acidic conditions; for example: treatment of **10** with HCO_2H and Et_3SiH 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]

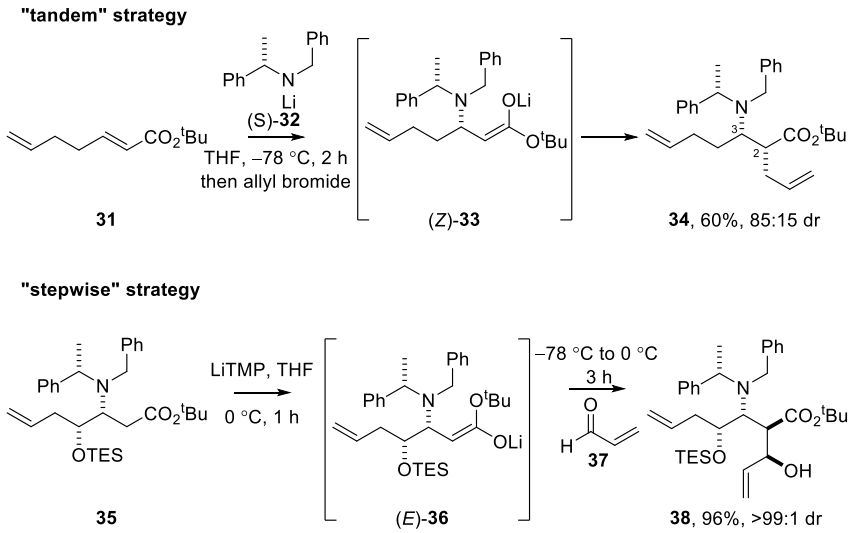


Scheme 2. Representative chemoselective *N*-deprotections [PMP = 4-methoxyphenyl; TDBMS = *tert*-butyldimethylsilyl]

α-Functionalisation of β-Amino Acid Derivatives

In order to expand the structural diversity of the accessible β-amino acid derivatives, α-functionalisation of the β-amino ester has been investigated. α-Functionalisation of the β-amino acid derivatives can be achieved via elaboration of the intermediate enolate resulting from

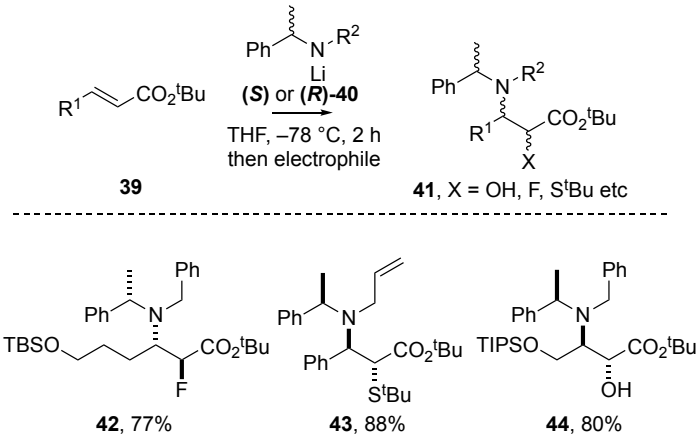
conjugate addition of a lithium amide reagent to an α,β-unsaturated ester with an electrophile (tandem manner). Alternatively, α-functionalisation can be achieved upon formation of the corresponding β-amino enolate upon deprotonation of a β–amino ester with a strong base (e.g., LDA, NaHMDS etc) followed 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 α,β-unsaturated ester **31** followed by the addition of allyl bromide to the intermediate lithium (Z)-β-amino enolate (*Z*)-**33** gave **34** in 60% yield as an 85:15 mixture of C(2)-epimers,[17] while treatment of β-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" α-functionalisation strategies

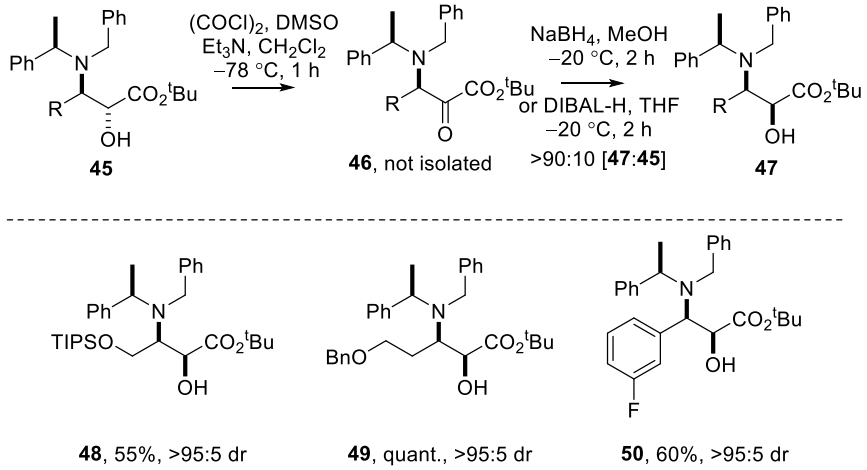
Treatment of β-amino enolates, derived from the conjugate addition of an enantiopure lithium amide **40** to an α,β-unsaturated ester **39**, with various electrophiles facilitated the preparation of a range of α-fluoro, α-mercapto, and α-hydroxy-β-amino acid derivatives **41**. For example, Duggan and co-workers reported the tandem conjugate addition/fluorination of α,β-unsaturated ester using the electrophilic fluorinating agent *N*-fluorobenzenesulfonimide (NFSI), which gave *anti*-α-fluoro-β-amino ester **42** in 77% yield.[19] Similarly, *anti*-α-*tert*-butylthio-β-amino ester **43** was obtained in 88% yield as a single diastereoisomer by in situ enolate trapping with TsS^tBu.[20] In situ enolate oxidation with

the requisite antipode of canmphorsulfonyloxaziridine (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. α-Functionalisation of β-amino enolates

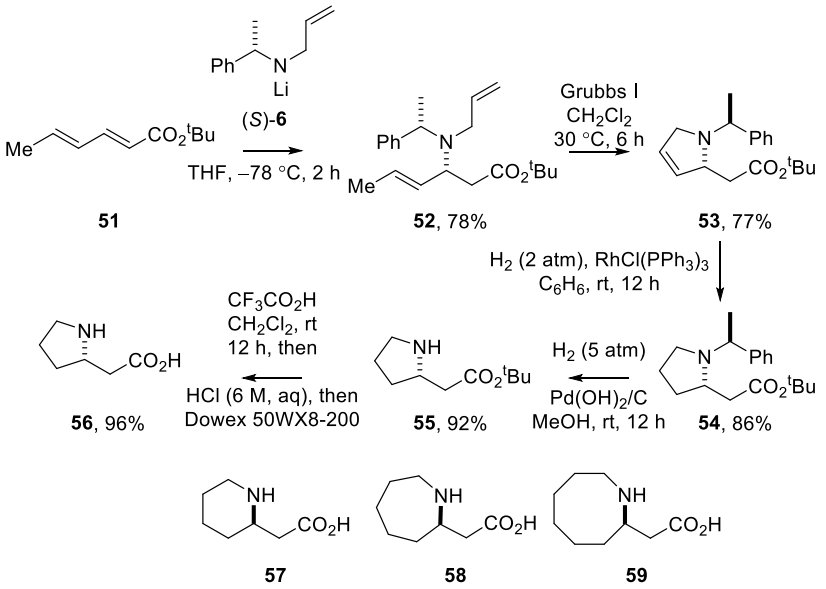
The corresponding *syn*-α-hydroxy-β-amino ester **47** can be prepared via an oxidation/diastereoselective reduction protocol.[23] For example, Swern oxidation of *anti*-α-hydroxy-β-amino ester **45** gives the corresponding ketone **46**, and reduction with either $NaBH_4$ in MeOH or DIBAL-H in THF 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

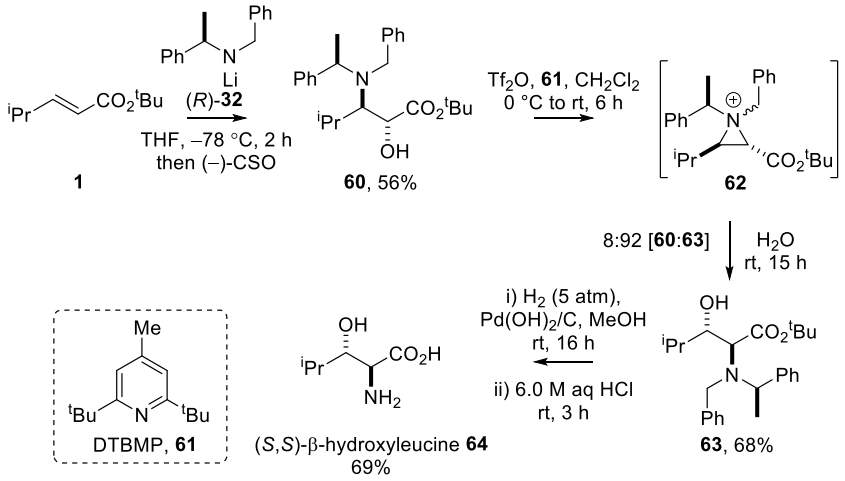
Preparations of enantiopure cyclic β-amino acids were also developed via conjugate addition of lithium *N*-allyl-*N*-(α-methylbenzyl)amide or lithium *N*-but-3-enyl-*N*-(α-methylbenzyl)amide to a suitable α,β-unsaturated ester followed by ring-closing metathesis as the key steps. For example, conjugate 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).[26] 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.[24,25] 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 Tf_2O 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 H_2O 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).[33] 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.[34]



Scheme 7. α-Amino acid synthesis via aziridinium rearrangement

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.

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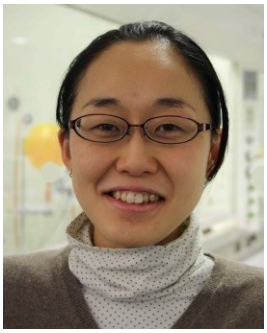

Ai Fletcher obtained a B. Eng. from Keio University, Japan, then moved to the U.K. where she pursued a Ph.D. at Imperial College London under supervision of Professor Chris Braddock. Since completing her Ph.D. in 2004, she has explored a range of chemistry as a post-doctoral researcher at the University 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.