Journal Name

ARTICLE

SuperQuat Chiral Auxiliaries: Design, Synthesis, and Utility

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

Received 00th January 20xx,
Accepted 00th January 20xx

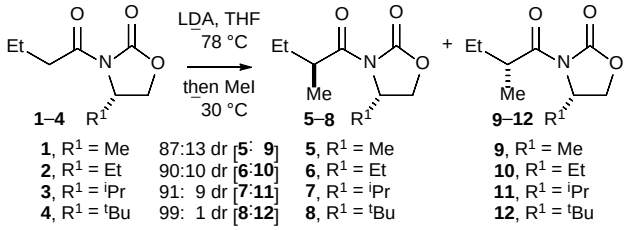
DOI: 10.1039/x0xx00000x

www.rsc.org/

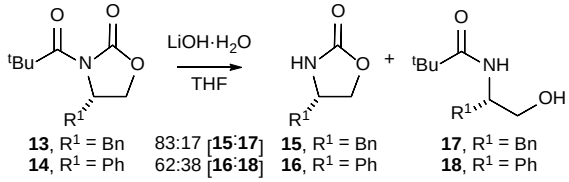
The SuperQuat (4-substituted 5,5-dimethyloxazolidine-2-one) family of chiral auxiliaries were first developed by us in the 1990s to address the shortcomings of the Evans (4-substituted oxazolidin-2-one) family of chiral auxiliaries. The incorporation of geminal dimethyl substitution at C(5) has two effects: (i) it induces a conformational bias on an adjacent, otherwise conformationally labile C(4)-substituent so that it projects towards the *N*-acyl fragment, thus offering superior diastereofacial selectivity in a range of transformations; and (ii) it hinders nucleophilic attack at the endocyclic carbonyl group, facilitating recovery and recyclability of the auxiliary, with enhanced cleavage properties. This review summarises the development and some of the most common uses of the SuperQuat family of chiral auxiliaries, particularly in the synthesis of natural products or other targets having bioloigcal interest. Where possible, comparisons with the performances of the corresponding Evans auxiliaries are presented.

Introduction

The potential of 4-substituted oxazolidin-2-ones to act as chiral auxiliaries was first demonstrated by Evans in 1981.[1] These so-called Evans auxiliaries proved to be attractive for a number of reasons and their utility in asymmetric synthesis has since been extensively documented and reviewed.[2–4] Briefly, they are popular for a number of reasons: (i) they are readily prepared, in enantiomerically pure form, from the corresponding α-amino acids (or pseudoephedrine); (ii) they are readily *N*-acylated with a range of activated carboxylic acid derivatives; (iii) they offer modest to good levels of diastereocontrol for a range of reactions of the pendant *N*-acyl fragment (including alkylations, aldol reactions, etc); (iv) the functionalised *N*-acyl fragment can be readily cleaved and the auxiliary recovered, facilitating recycling. Nonetheless, there are some shortcomings associated with the use of Evans auxiliaries. Firstly, the relatively high conformational freedom of the C(4)-substituent means that very high diastereoselectivity is often only achievable with a very sterically demanding C(4)-*tert*-butyl group derived from L-*tert*-leucine, a non-naturally occurring amino acid which is prohibitively expensive to use on a large scale. This is illustrated upon inspection of the diastereoselectivites of the methylations of the *N*-butanoyl Evans derivatives **1–4**, having oxazolidin-2-ones with C(4)-stereodirecting groups of increasing steric demand (R^1 = Me, Et, ^{i}Pr, ^{t}Bu): the diastereoselectivites of the reactions of **1–3** (R^1 = Me, Et, ^{i}Pr) are very similar (≈90:10 dr), with significantly higher levels of diastereoselectivity being noted only for reaction of **4** (R^1 = ^{t}Bu), which gives the diastereoisomeric products **8** and **12** in 99:1 dr[5] (Scheme 1). Secondly, during the cleavage step, there is a propensity for the endocyclic carbonyl group to be attacked, leading to unwanted cleavage products which both diminish the yield of the desired carboxylic acid derivative and hamper recovery and recycling of the chiral auxiliary. A severe case of this effect is noted upon hydrolysis of the *N*-pivaloyl derivatives **13** and **14**, which give 17% and 38% of the endocyclic cleavage pathways leading to production of **17** and **18**, respectively, as unwanted by products[6] (Scheme 2).



Scheme 1 Methylation of *N*-butanoyl Evans derivatives **1–4**.



Scheme 2 Hydrolysis of *N*-pivaloyl Evans derivatives **13** and **14**.

In 1995 we introduced 4-substituted oxazolidin-2-ones with geminal dimethyl substitution at C(5) to the arena;[7] these were dubbed SuperQuat auxiliaries.[8] In designing the SuperQuat auxiliaries, we anticipated that the incorporation of geminal C(5)-substitution would confer twofold benefits to the parent Evans oxazolidinones: (i) steric considerations would mean that an otherwise conformationally labile C(4)-

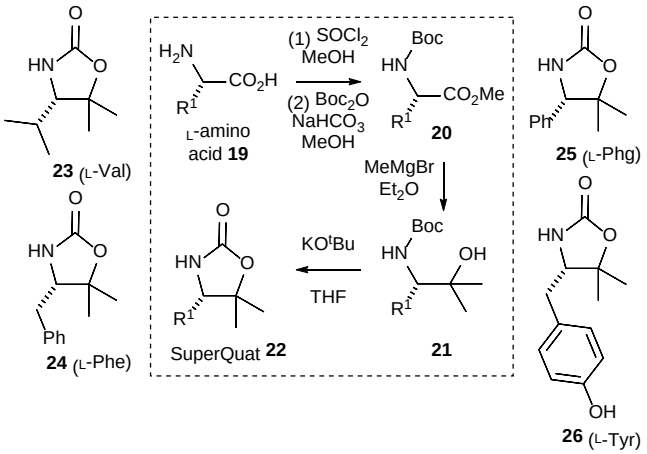
Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, OX1 3TA, UK. E-mail: steve.davies@chem.ox.ac.uk

stereodirecting group (e.g., benzyl or isopropyl) should be caused to project towards the *N*-acyl fragment, offering improved diastereofacial bias that would be manifest in increased reaction diastereoselectivity; (ii) the trajectory for attack on the endocyclic carbonyl group would be hindered, reducing the proclivity for endocyclic cleavage. We chose to incorporate geminal C(5)-dimethyl substitution into our auxiliary to result in the lowest possible molecular weight for such an auxiliary. Subsequent notable contributions to the field were made from 1998 onwards by Gibson et al.[9] and then Seebach et al.,[10–13] who established 4-substituted oxazolidin-2-ones with geminal C(5)-diphenyl substitution functioned as equally effective chiral auxiliaries (offering improved levels of diastereoselectivity over their Evans counterparts) in a range of reactions. In an effort to provide specific illustration of the benefits of using a geminally C(5)-disubstituted auxiliary, as compared to its C(5)-unsubstituted (Evans) counterpart, this review focuses on the preparation and basic aspects of use of SuperQuat auxiliaries in synthesis, followed by a brief discussion of representative synthetic applications.[14] These examples are chosen to encompass the most common reaction types in which these auxiliaries are employed, and wherever possible data to enable direct comparison between the different auxiliaries is given. In each case, models which have been developed to rationalise (and thence can be used to predict) the observed diastereoselectivity are given; selected examples to demonstrate either reaction scope or utility in target synthesis are also included.

Discussion

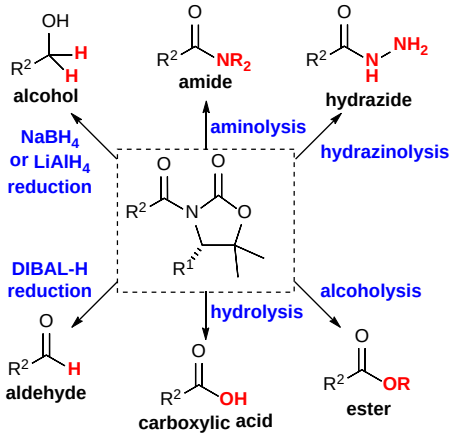
Basics: Synthesis, Acylation and Cleavage

SuperQuat auxiliaries are conveniently prepared from the parent α-amino acid via our simple four-step procedure which requires no chromatography; a final recrystallization provides analytically pure material.[8] Treatment of the parent α-amino acid **19** with $SOCl_2$ in MeOH gives the corresponding methyl ester hydrochloride salt which is treated with Boc_2O to give the corresponding *N*-Boc protected methyl ester **20**. Addition of excess MeMgBr gives the tertiary alcohol **21** which is cyclised to give the corresponding SuperQuat auxiliary that can be purified by recrystallization.[8,15] (Scheme 3). The most commonly employed SuperQuat auxiliaries for asymmetric synthesis are L-Val-derived **23**, L-Phe-derived **24** and L-Phg-derived **25**. We have also investigated L-Tyr-derived **26** (as an analogue of L-Phe-derived **24**) that can be attached to solid phase.[16,17]

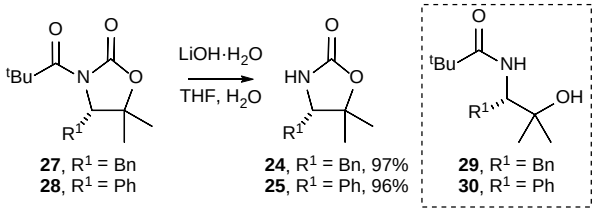


Scheme 3 Synthesis of SuperQuat auxiliaries.

Use of SuperQuat auxiliaries in synthesis usually entails *N*-acylation, subsequent diastereoselective functionalisation, and then cleavage to give the requisite enantiopure products. *N*-Acylation of SuperQuat auxiliaries can be very simply achieved by treatment of the auxiliary with BuLi in THF followed by the addition of the requisite acid chloride or anhydride. The desired diastereoselective transformation(s) is (are) then performed before cleavage from the auxiliary. An *N*-acyl SuperQuat functions as an activated acyl donor for reaction with a range of nucleophiles (Scheme 4). The presence of the geminal C(5)-dimethyl functionality confers adequate shielding to the endocyclic carbonyl functionality and, for example, in direct contrast to the behaviour of the *N*-pivaloyl Evans derivatives **13** and **14**[6] (Scheme 2), under identical conditions the *N*-pivaolyl SuperQuat derivatives **27** and **28** undergo hydrolysis with LiOH to regenerate the parent auxiliaries L-Phe **24** and L-Phg **25** exclusively[6] (Scheme 5).



Scheme 4 Cleavage pathways for *N*-acyl SuperQuat derivatives.



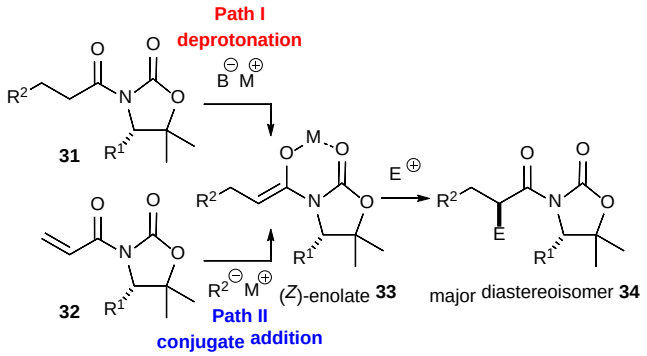
Scheme 5 Hydrolysis of *N*-pivaloyl SuperQuat derivatives **27** and **28** (represented in the same enantiomeric series for ease of comparison).

Diastereoselective Reactions of *N*-Acyl SuperQuat Derivatives

The following sections summarise some of the most common types of diastereoselective functionalisations of *N*-acyl SuperQuat derivatives.[14] Sections are arranged to illustrate the ability of the SuperQuat auxiliary to control the formation of one or two new stereogenic centres at the α-, β- and/or β′-position(s) of the *N*-acyl fragment of the product.

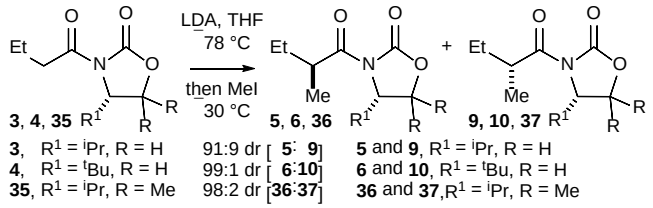
Stereoinduction at the α-Carbon

Enolate Alkylation. Enolates of *N*-acyl SuperQuats are most often formed via deprotonation of the parent *N*-acyl SuperQuat **31** (Path I) but have also been generated via conjugate addition to an *N*-acryloyl SuperQuat **32** (Path II). The diastereoselectivity of the enolate functionalisation can be rationalised by invoking the intermediate (*Z*)-enolate **33**, which resides in the chelated conformer with the counterion between the two oxygen atoms, holding the two C–O bonds parallel; subsequent electrophilic attack on this conformer occurs preferentially on face of the enolate opposite to the C(4)-stereodirecting group, to give the major diastereoisomeric product **34** (Scheme 6).

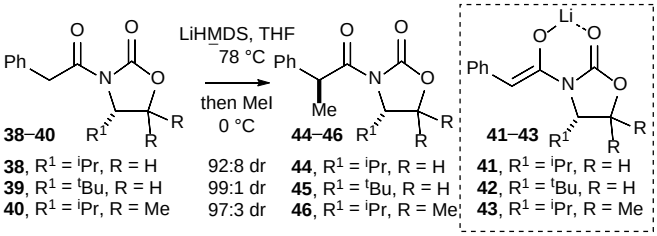


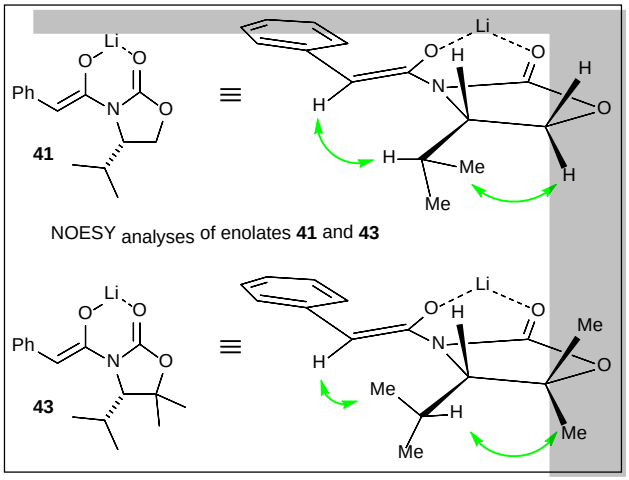
Scheme 6 Methods for enolate generation. Type I: Deprotonation of *N*-acyl SuperQuat derivatives. Type II: Conjugate addition to *N*-acryloyl SuperQuat derivatives.

Type I: Enolates via Deprotonation. α-Alkylation of *N*-acyl SuperQuat enolates provides a simple example of the superior levels of diastereoselectivity that are available when using a SuperQuat auxiliary compared to its Evans counterpart. For example, methylation of the enolate of *N*-butanoyl L-Val-SuperQuat derivative **35** gives **36** in 98:2 dr;[18] higher than the diastereoselectivity of L-Val-Evans derivative **3** and comparable with that of L-Tle-Evans derivative **4** under identical conditions (Scheme 7). We have established that the use of L-Val-SuperQuat **23** in a range of reactions results in high levels of diastereoselectivity being observed which are usually only obtainable when using L-Tle-Evans in the C(5)-unsubstituted series of oxazolidinones;[18,19] the former is prepared from inexpensive L-Val (or a derivative) whilst the latter is prepared from the more costly L-Tle (or a derivative), limiting its use on scale for economic reasons. The levels of stereocontrol are consistent with the decreased conformational freedom imposed on the C(4)-alkyl group by the geminal C(5)-dimethyl substitution rendering the isopropyl group within a SuperQuat auxiliary an effective mimic for a *tert*-butyl group within an Evans auxiliary. Indeed, when investigating methylation of the *N*-phenacyl oxazolidin-2-one derivatives **38–40**, ^{1}H NMR NOESY analysis (at low-temperature) of the intermediate enolate **41** (derived from *N*-acyl Evans **38**) revealed strong reciprocal correlations between C(5)*H* and C(4)CH*Me*$_2$, and between C(2′)*H* and C(4)C*H*Me$_2$; moreover, no correlations were observed between C(5)*H* and C(4)C*H*Me$_2$, nor between C(2′)*H* and C(4)CH*Me*$_2$, entirely supportive of a conformation in which the steric bulk of the isopropyl unit is projected towards the auxiliary (rather than the *N*-acyl enolate fragment). In contrast, the same analysis of enolate **43** (derived from *N*-acyl SuperQuat **40**) revealed a series of complementary NOESY correlations (and lack thereof) which were consistent with a conformation in which the steric bulk of the isopropyl unit is projected towards the *N*-acyl enolate fragment. This is entirely consistent with the observation of higher diastereoselectivity when using the SuperQuat auxiliary as compared with its Evans counterpart, with **46** being formed in 97:3 dr compared to **44** being formed in 92:8 dr, and is furthermore consistent with the isopropyl group within **40** mimicking the *tert*-butyl group within **39** as upon methylation of the latter, **45** is formed in 99:1 dr[18,19] (Scheme 8).



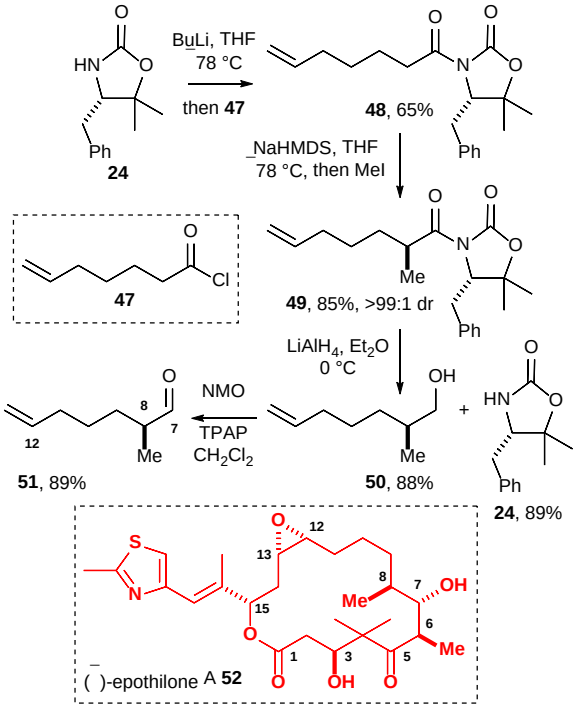
Scheme 7 L-Val-SuperQuat as an L-Tle-Evans mimic. Methylation of *N*-butanoyl oxazolidin-2-one derivatives **3**, **4** and **35** (represented in the same enantiomeric series for ease of comparison).





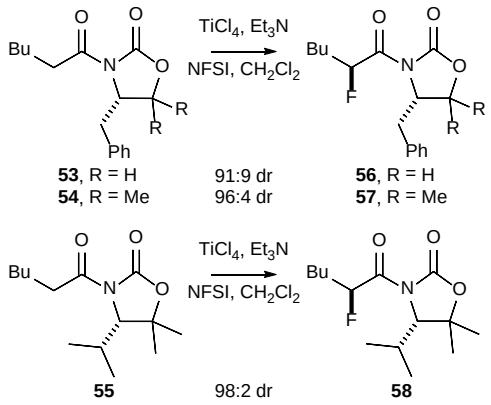
Scheme 8 L-Val-SuperQuat as an L-Tle-Evans mimic. Methylation of *N*-α-phenacyl oxazolidin-2-one derivatives **38**–**40** (represented in the same enantiomeric series for ease of comparison).

α-Alkylations such as these have found application in natural product syntheses. For example,[20] aldehyde **51** was required by Schinzer *et al.* in their synthesis of (−)-epothilone A **52**. This was prepared using methylation of L-Phe SuperQuat derivative **48** as the key step. Treatment of **48** with NaHMDS then MeI gave **49** in 85% yield as a single diastereoisomer. Reductive cleavage of **49** was achieved using $LiAlH_4$ and alcohol **50** was isolated in 88% yield, alongside recovered L-Phe SuperQuat **24** in 89% yield. Subsequent oxidation of alcohol **50** furnished aldehyde **51**, which ultimately provided the C(7)–C(12) fragment of the macrolactone ring of **52** (Scheme 9).[21]



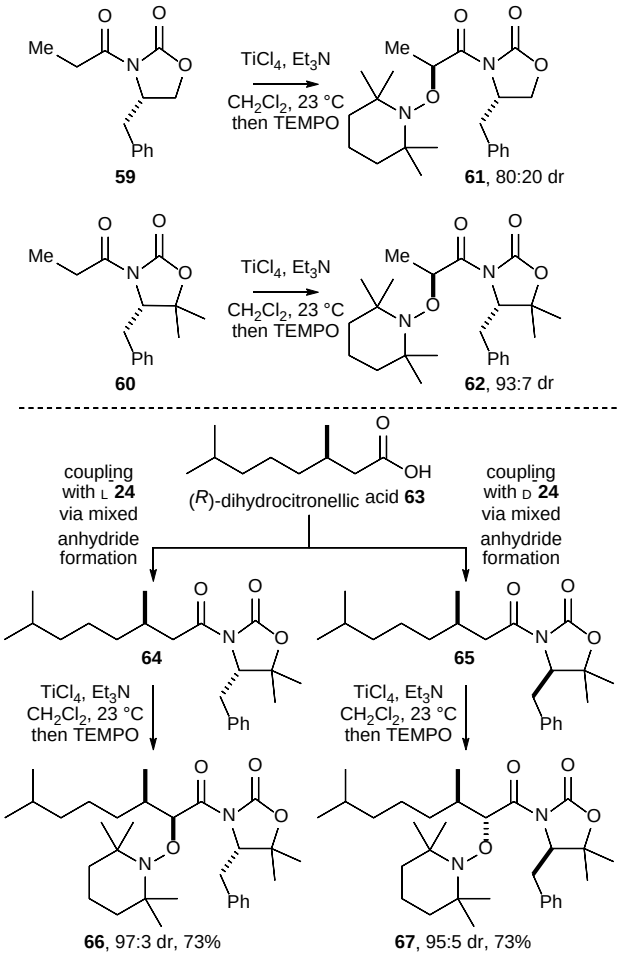
Scheme 9 α-Alkylation. Synthesis of (−)-epothilone A **52**.

Zakarian *et al.* reported that treatment of *N*-acyl SuperQuats with $TiCl_4$, Et_3N and NFSI enabled α-fluorination.[22] L-Phe-Evans derivative **53** and L-Phe-SuperQuat derivative **54** was reported to give the corresponding products **56** and **57** in 91:9 dr and 96:4 dr, respectively, although L-Val-SuperQuat derivative **55** delivered **58** in 98:2 dr (Scheme 10). This procedure proved general for a range of L-Val-SuperQuat derivatives of aliphatic carboxylic acids; use of $Ti(O^iPr)_2Cl_2{\cdot}2Et_3NHCl$ as the Lewis acid enabled α-fluorination of a range of L-Val-SuperQuat derivatives of aromatic and heteroaromatic carboxylic acids. Two representative examples of cleavage (reduction and hydrolysis) to give the corresponding fluorinated building blocks proceeded without loss of stereochemical integrity.



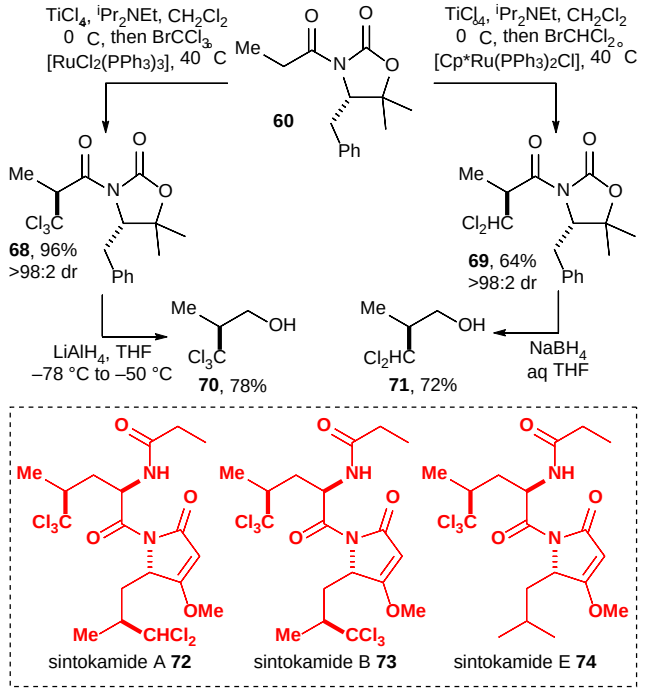
Scheme 10 α-Fluorination of *N*-acyl oxazolidin-2-one derivatives.

Zakarian *et al.* also developed an α-aminooxylation protocol upon treatment of *N*-acyl SuperQuats with $TiCl_4$ and Et_3N, then TEMPO.[23] It was proposed that the in situ formed titanium enolate undergoes oxidation upon introduction of TEMPO; ensuing radical-radical coupling with TEMPO then gives the α-aminooxylated product. Reaction optimisation showed that L-Phe-Evans **59** gave α-aminooxylated product **61** in 80:20 dr whereas L-Phe-SuperQuat **60** gave α-aminooxylated product **62** in 93:7 dr (Scheme 11). Zakarian *et al.*,[23] and later Romea, Urpí, *et al.*,[24] established the generality of this procedure for a range of *N*-acyl L-Phe-SuperQuat derivatives. Representative examples of cleavage (reduction or methanolysis) to liberate the α-functionalised products were also included in these studies.[23,24] The substrates investigated included the diastereoisomeric *N*-acyl SuperQuats **64** and **65** [derived from coupling enantiopure (*R*)-dihydrocitronellic acid **63** with both L-Phe-SuperQuat L-**24** and D-Phe-SuperQuat D-**24**]: α-aminooxylation of **64** and **65** proceeded to give adducts **66** and **67** in 97:3 dr and 95:5 dr, respectively, and in 73% isolated yield in both cases, indicating that the stereochemical outcomes of these reactions are dictated predominantly by the stereoinduction of the SuperQuat fragment in both cases, with the relative configuration of the β-stereocentre having little effect[23] (Scheme 11).



Scheme 11 α-Aminooxylation of *N*-acyl oxazolidin-2-one derivatives.

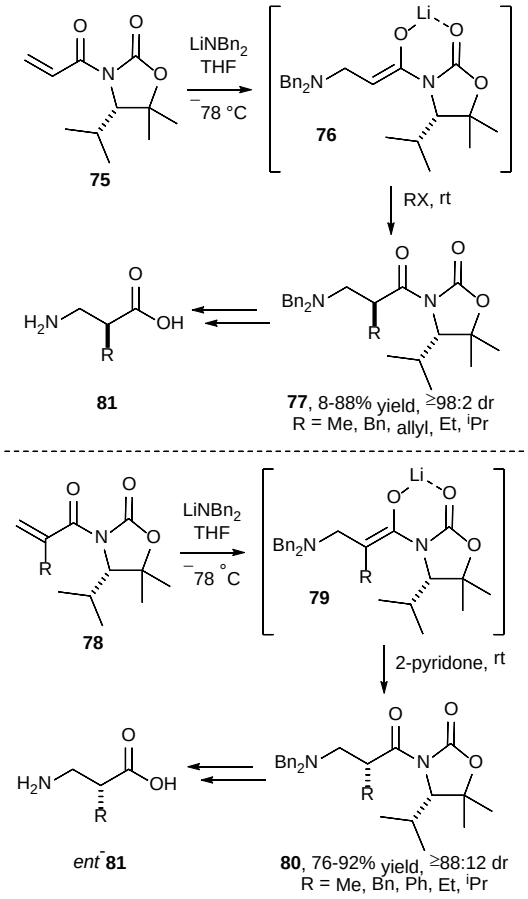
Zakarian *et al.* also reported related (i.e., radical mediated) methods for haloalkylation of *N*-acyl SuperQuat enolates,[25,26] which they deployed in a unified synthesis of sintokamides A **72**, B **73** and E **74**.[27] Trichloromethylation of **60** was achieved upon treatment with $TiCl_4$ and $^iPr_2NEt$, then $[RuCl_2(PPh_3)_3]$ and $BrCCl_3$, giving **68** as a single diastereoisomer in 96% yield. Reduction of **68** with $LiAlH_4$ provided alcohol **70** in 78% yield. Similarly, dichloromethylation of **60** was achieved upon treatment with $TiCl_4$ and $^iPr_2NEt$, then $[Cp^*Ru(PPh_3)_2Cl]$ and $BrCHCl_2$, giving **69** as a single diastereoisomer in 64% yield. Reduction of **69** with $NaBH_4$ gave alcohol **71** in 72% yield. Further elaboration of **70** and **71** (including a series of peptide couplings) completed assembly of the natural products **72**–**74** (Scheme 12).



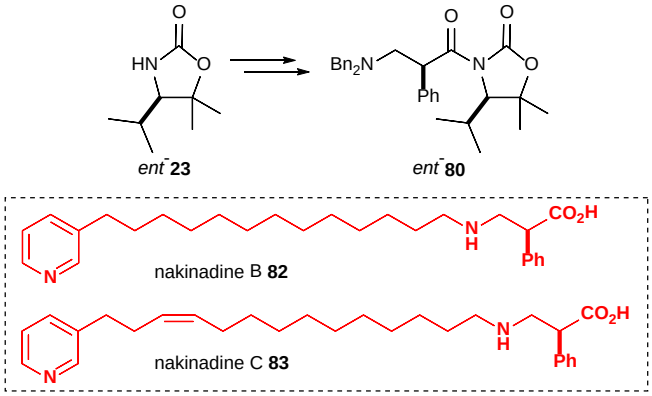
Scheme 12 α-Dichloromethylation and α-trichloromethylation. Synthesis of sintokamide A **72**, sintokamide B **73**, and sintokamide E **74**.

Type II: Enolates via Conjugate Addition. In continuation of our interest in the synthesis of β-amino acids, we developed a synthesis of β²-amino acids, reliant on the conjugate addition of lithium dibenzylamide to *N*-acryloyl SuperQuat **75**, generating an intermediate (*Z*)-enolate **76** which was subsequently alkylated, as the key step.[28,29] As may be expected, the efficacy of the alkylation reaction was influenced by the relative reactivity of the alkylating agent to an S_N2-type process: methyl iodide, benzyl bromide and allyl bromide provided the corresponding products **77** (R = Me, Bn and allyl) in 92%, 82% and 88% yield, respectively, whereas ethyl iodide and isopropyl iodide gave the corresponding products **77** (R = Et and ^{i}Pr) in 62% and 8% yield, respectively; in all cases, however, the diastereoselectivity was very high (≥98:2 dr). Importantly, in comparison to *N*-acryloyl SuperQuat **75** (R = Me) which gave adduct **77** (R = Me) in 92% yield, reaction of the corresponding *N*-acryloyl Evans derivative resulted in formation of polymeric material and delivered the desired adduct in only 66% yield. Methanolysis and hydrogenolysis of **77** gave access to the corresponding β²-amino acids **81** in good yield, without loss of stereochemical integrity. A strategy involving conjugate addition with ensuing diastereoselective enolate protonation was also developed to facilitate a more general synthesis of the same targets.[28,29] Addition of lithium dibenzylamide to *N*-acryloyl SuperQuats **78** (having α-substituents), followed by addition of 2-pyridone as the proton source furnished **80** in 76–92% yield and ≥88:12 dr. As **77** and **80** are diastereoisomeric (related as epimers at the α-stereocentre), deprotection of **80** gives the corresponding enantiomeric β²-amino acids *ent*-**81**, again without loss of the stereochemical integrity (Scheme 13). This methodology is complementary to our conjugate addition/alkylation strategy

applied to the parent α-acryloyl SuperQuat **75** as it allows the synthesis of the enantiomeric forms of β²-amino acids **81** from the same enantiomer of Val-derived (in this case L-Val derived) SuperQuat **23**, with the added advantage that it is applicable to the synthesis of β²-amino acids **81** that are not efficiently accessible via enolate alkylation, as well as those incorporating α-aryl groups. The latter facet of this approach enabled its use in the first asymmetric syntheses of the alkaloids nakinadine B **82**[30] and nakinadine C **83**[31] from D-Val derived **23** (Scheme 14).

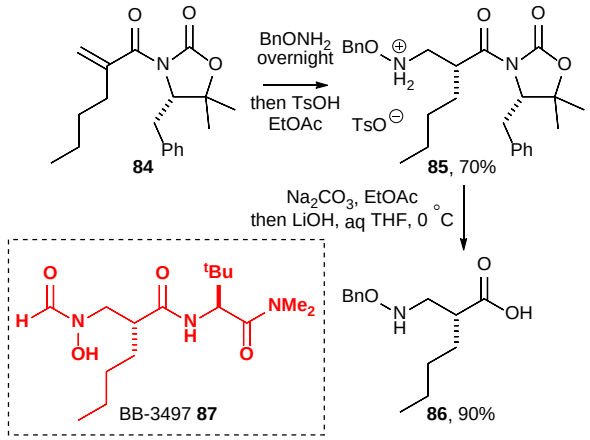


Scheme 13 Conjugate addition/enolate alkylation and conjugate addition/enolate protonation. Synthesis of β²-amino acids.



Scheme 14 Conjugate addition/α-protonation. Synthesis of nakinadine B **82** and nakinadine C **83**.

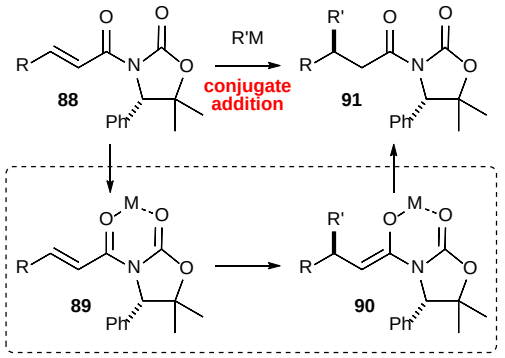
Pratt *el al.* reported a route to BB-3497 **87**, a potent peptide deformylase inhibitor, using a related approach.[32] Addition of *O*-benzylhydroxylamine to *N*-(α-butylacryloyl) SuperQuat **84** (prepared in 85% yield by coupling of L-Phe **24** with the requisite mixed anhydride) at room temperature overnight gave **85** in >95:5 dr, with formation of the tosylate salt **85**·TsOH and recrystallization providing **85**·TsOH as a single diastereoisomer in 70% yield. Sequential basification of the salt and cleavage of the auxiliary via saponification gave **86**. Elaboration of **86** (via sequential *N*-formylation, coupling with *tert*-leucine *N*,*N*-dimethylamide and *O*-debenzylation) then provided the target **87** (Scheme 15).



Scheme 15 Conjugate addition/enolate protonation. Synthesis of BB-3497 **87**.

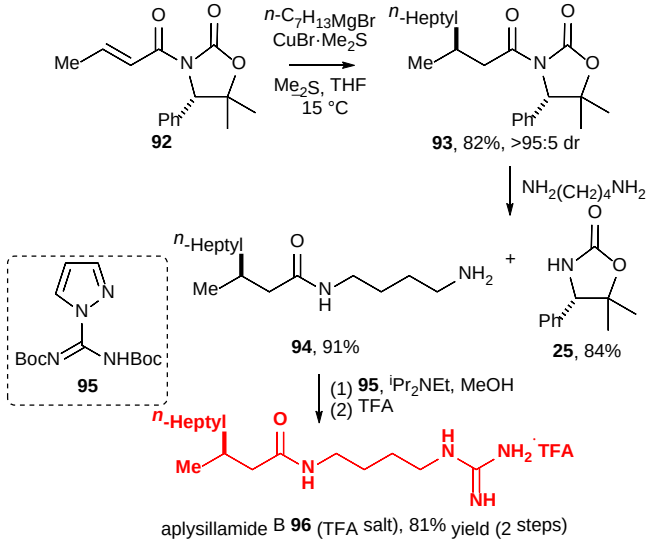
Stereoinduction at the β-Carbon

Conjugate Addition. We demonstrated that the conjugate additions of organocopper reagents to an α,β-unsaturated *N*-acyl L-Phg-SuperQuat derivatives **88** proceed with very high diastereoselectively to give the corresponding β-functionalised products.[6,7,33] In contrast to the use of derivatives of L-Phg-SuperQuat **25**, use of L-Val-SuperQuat **23** or L-Phe-SuperQuat **24** in this reaction manifold results in significantly poorer levels of diastereoselectivity.[6] A similar trend is noted using the analogous *N*-acyl Evans auxiliaries[34] although the reasons for this disparity are unclear. The stereochemical outcome for such reactions is, however, consistent with delivery of the carbanion nucleophile to the least hindered face of **89**: chelation with a metal ion holds the two carbonyl groups parallel and activates the system as an electrophile, whilst the α,β-unsaturated system preferentially resides in the *s-cis* conformation to reduce steric interaction with the SuperQuat auxiliary. Conjugate addition to **89** results in formation of the corresponding (*Z*)-enolate **90**, which upon protonation gives **91** (Scheme 16).



Scheme 16 Conjugate addition to α,β-unsaturated *N*-acyl L-Phg-SuperQuat derivatives **88**.

This transformation was used by us as one of the key steps in an asymmetric synthesis of aplysillamide B **96**.[6] Conjugate addition of the organocuprate derived from *n*-heptylmagnesium bromide and CuBr to **92** gave **93** in >95:5 dr, which was isolated in 82% yield. Aminolysis using 1,4-diaminobutane gave the corresponding amide **94** directly, in 91% isolated yield, and recovered L-Phg-SuperQuat **25** in 84% yield. Guanidylation of **94** using guanidylating agent **95** followed by *N*-Boc deprotection using TFA gave aplysillamide B **96** (as the TFA salt) in 81% yield over the 2 steps (Scheme 17).[35]

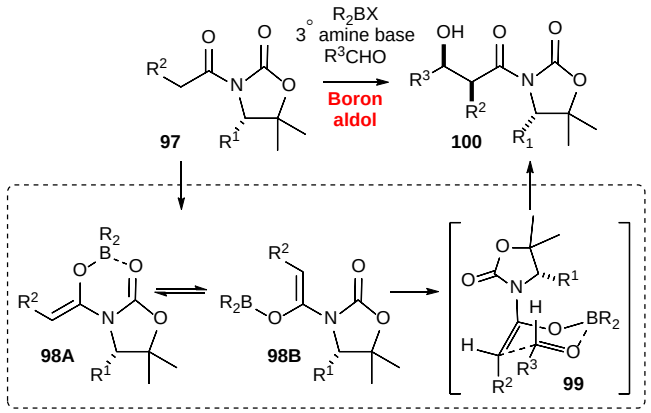


Scheme 17 Conjugate addition. Synthesis of aplysillamide B **96**.

Interestingly, Lei *et al.* demonstrated that conjugate addition of an organocopper reagent followed by treatment with *N*-bromosuccinimide resulted in *cis*-addition of the organometallic fragment and a bromine atom to the carbon-carbon double bond; the stereochemical outcome of functionalisation of the intermediate (*Z*)-enolate **90** at the α-centre is thus as previously described[36] (Scheme 6).

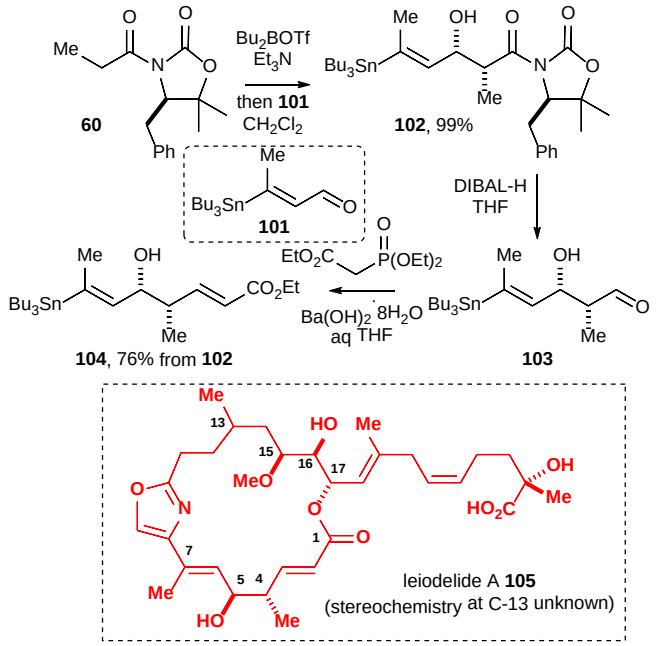
Stereoinduction at the α- and β'-Carbons

Enolate Aldol Reactions. Alongside enolate alkylation, perhaps the other archetypal reaction of *N*-acyl oxazolidinone auxiliaries is the enolate aldol reaction. High stereoselectivity in these reactions is most commonly achieved using a boron enolate, generated directly from treatment of the requisite *N*-acyl SuperQuat **97** with R_2BX (Bu_2BOTf, 9-BBN-OTf, etc) in the presence of a tertiary amine base (Et_3N, $^iPr_2NEt$, etc) to generate the corresponding boron (*Z*)-enolate **98** in situ. Co-ordination of the aldehyde to the boron atom requires disruption of the chelated conformation **98A** of the enolate such that the non-chelated form **98B**, in which the dipoles associated with the C–O bonds are opposed, becomes the reactive one. Attack on the aldehyde then occurs on the face of the enolate opposite to the stereodirecting group (R^1) of the SuperQuat, and proceeds via a Zimmerman-Traxler-type transition state **99** in which the aldehydic substituent (R^3) preferentially occupies an equatorial site. This gives rise to the corresponding *syn*-aldol product **100**.[37] Although the α-substituent (R^2) is commonly a hydrocarbon, α-alkoxy,[38–41] α-dibenzylamino[39] and α-halo[42] substituents have also been accommodated in this reaction. An analogous stereochemical outcome is produced when the titanium(IV) enolate, generated in situ from treatment of the requisite *N*-acyl SuperQuat **97** with $TiCl_4$ in the presence of a tertiary amine base, is employed to enable the reaction (Scheme 18).



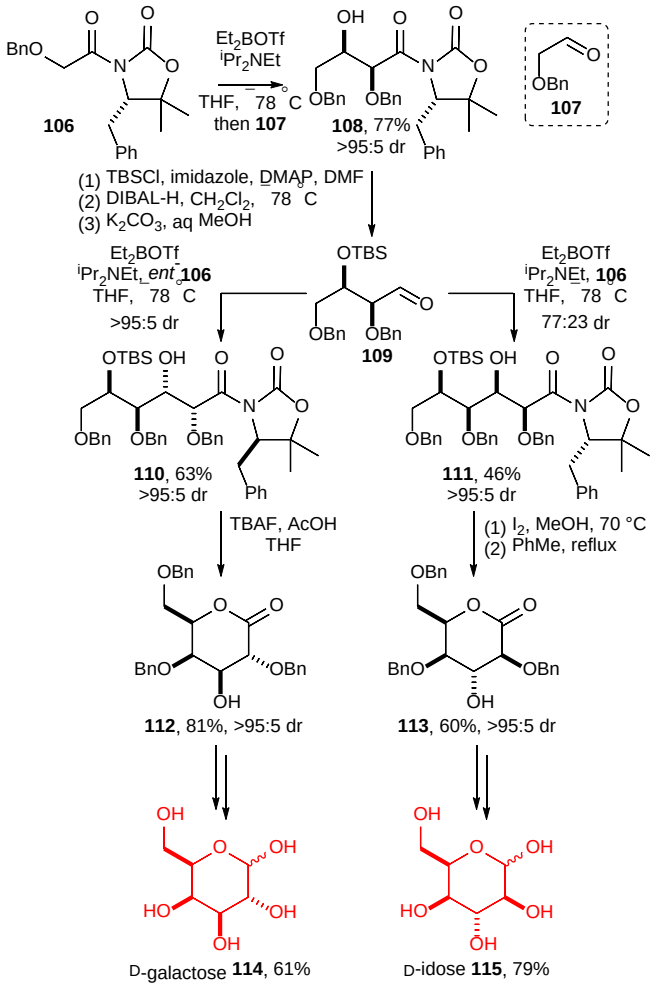
Scheme 18 *syn*-Selective boron enolate aldol reaction of *N*-acyl SuperQuats **97**.

Aldol reactions such as these have been deployed in studies directed toward the synthesis of complex natural products. For example, Stambuli *et al.* employed boron enolate aldol reaction of *N*-propionyl D-Phe SuperQuat **60** with aldehyde **101** to give *syn*-aldol product **102** in 99% yield. Reduction with DIBAL-H then provided aldehyde **103** directly, which was employed in a Wadsworth-Emmons olefination reaction to give **104** in 76% yield from **102**. It was proposed that this represented the "southern sub-unit" of the natural product leiodelide A **105**[43] (Scheme 19).



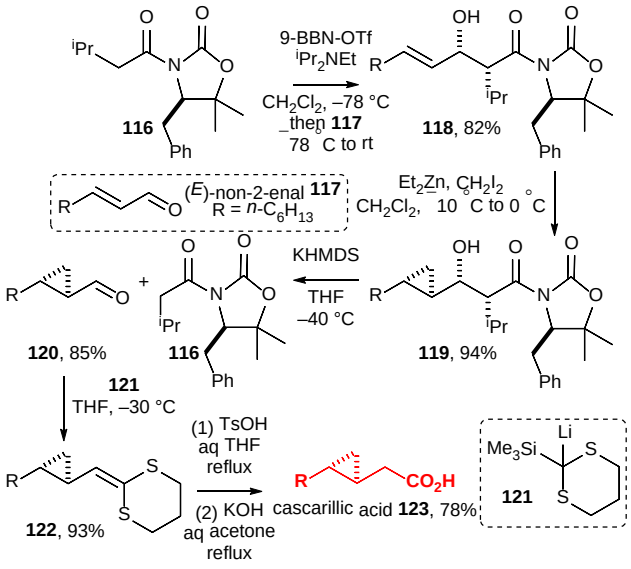
Scheme 19 Boron aldol reaction of *N*-acyl SuperQuat enolates. Towards leiodelide A **105**.

We employed iterative boron enolate aldol reactions (including glycolate aldol reactions) to facilitate the synthesis of a number of hexose monosaccharides, including D-galactose **114** and D-idose **115**.[38,41] Treatment of *N*-α-benzyloxyacetyl L-Phe SuperQuat **106** with aldehyde **107** gave *syn*-aldol product **108** as a single diastereoisomer in 77% yield. Sequential *O*-silylation and reduction gave the corresponding stable hemiaminal, which liberated aldehyde **109** upon treatment with K_2CO_3 in MeOH. Doubly diastereoselective aldol reactions between aldehyde **109** and the enantiomers of *N*-acyl Phe SuperQuat **106** were then used to construct the remaining two stereogenic centres required for the hexose targets. Reaction of aldehyde **109** with *N*-α-benzyloxyacetyl D-Phe SuperQuat *ent*-**106** was the "matched" case,[44] and gave *syn*-aldol product **110** in >95:5 dr. Meanwhile, reaction of aldehyde **109** with *N*-α-benzyloxyacetyl L-Phe SuperQuat **106** was the "mismatched" case,[44] giving *syn*-aldol product **111** as the major product, in 77:23 dr. Chromatography allowed isolation of **111** as a single diastereoisomer (>95:5 dr) in 46% yield. Thus, the SuperQuat fragment **106** (and not the aldehyde **109**) is the dominant stereocontrolling factor even in the "mismatched" reaction. *O*-Desilylation and cyclisation of both **110** and **111** gave the corresponding lactones **112** and **113** as single diastereoisomers, which underwent reduction and hydrogenolytic deprotection to give D-galactose **114** and D-idose **115**, respectively (Scheme 20).



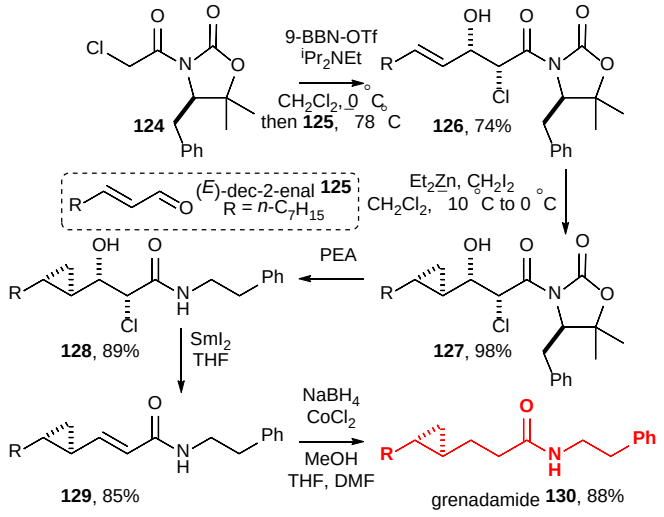
Scheme 20 Boron aldol reaction of *N*-acyl SuperQuat enolates. Synthesis of the hexoses D-galactose **114** and D-idose **115**.

Bull *et al.* developed an aldol, directed cyclopropanation, and reverse aldol reaction sequence to enable the synthesis of enantiopure cyclopropane-containing targets.[45] This approach was used in an asymmetric synthesis of cascarillic acid **123**.[46] Thus, aldol reaction of the boron enolate of **116** with (*E*)-non-2-enal **117** gave **118** as a single diastereoisomer in 82% yield. Cyclopropanation of **118** under modified Furukawa conditions gave cyclopropane **119** as a single diastereoisomer in 94% yield (the stereochemical outcome being consistent with a hydroxyl-directed process proceeding via a transition state in which 1,3-allylic strain is minimised). Treatment of **119** with KHMDS effected reverse aldol reaction to give aldehyde **120** in 85% yield alongside the *N*-acyl SuperQuat **116**. Aldehyde **120** was then reacted with **121** (formed in situ upon deprotonation of 2-trimethylsilyl-1,3-dithiane with BuLi), which resulted in sequential 1,2-addition and Peterson-type olefination to give **122** in 93% yield. Sequential acid-mediated and base-mediated hydrolyses then liberated cascarillic acid **123** in 78% yield (Scheme 21).



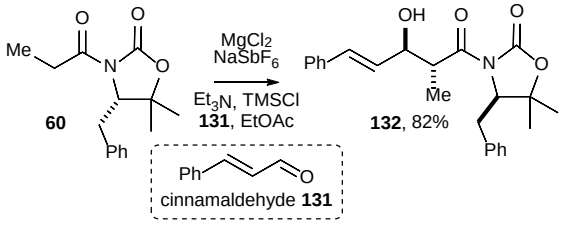
Scheme 21 Boron aldol reaction of *N*-acyl SuperQuat enolates. Synthesis of cascarillic acid **123**.

Bull *et al.* employed a similar approach in an asymmetric synthesis of grenadamide **130**.[42] Aldol reaction of *N*-α-chloroacetyl SuperQuat **124** (simply prepared by acylation of L-Phe SuperQuat **24** with chloroacetyl chloride) with (*E*)-dec-2-enal **125** gave **126**. Directed cyclopropanation then gave **127**. Treatment of **127** with phenethylamine (PEA) gave amide **128** directly. Subsequent treatment of **128** with SmI_2 effected elimination to give α,β-unsaturated amide **129** in 85% yield, and conjugate reduction of **129** was achieved using $NaBH_4$ and catalytic $CoCl_2$ to give grenadamide **130** in 88% yield (Scheme 22).[47]



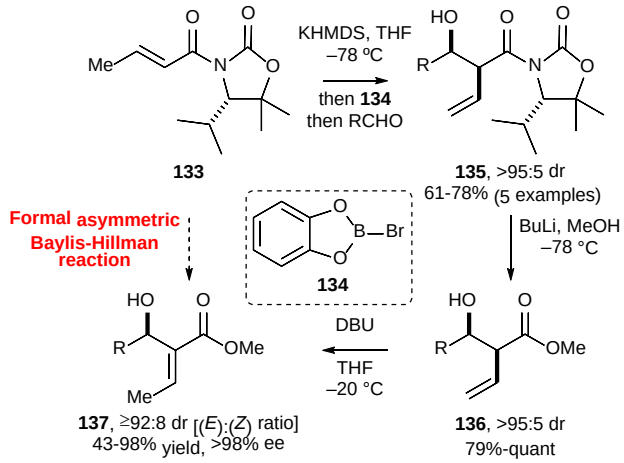
Scheme 22 Boron aldol reaction of *N*-acyl SuperQuat enolates. Synthesis of grenadamide **130**.

It should be noted that an alternative method to enable preparation of aldol adducts with relative *anti*-stereochemistry has been shown to be available when using the magnesium enolate,[48] although this has yet to find general employment within the geminally disubstituted oxazolidin-2-one family, with reactions of only a limited number of substrates (e.g., reaction of **60** with cinnamaldehyde **131**) having been investigated[49,50] (Scheme 23).



Scheme 23 *anti*-Selective magnesium enolate aldol reaction of an *N*-acyl SuperQuat.

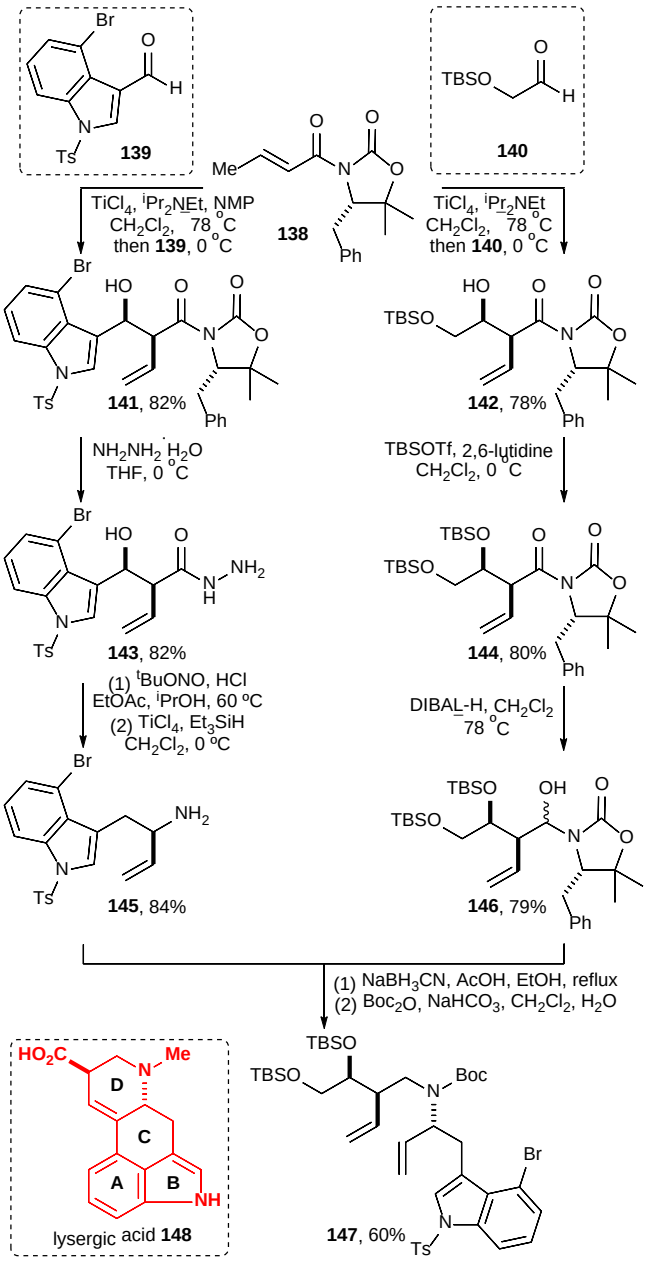
Dienolate Aldol Reactions. Aldol reactions also encompass reactions involving dienolates, which can be generated from the γ-deprotonation of *N*-crotonoyl SuperQuat derivatives. These boron and titanium dienolates behave in exactly the same manner as their (mono)enolate counterparts in the subsequent aldol reaction to give *syn*-aldol products of the type **100** where R^2 = vinyl (Scheme 18). For example, we used the boron dienolate aldol reaction of L-Val derived *N*-crotonoyl SuperQuat **133** to enable a formal asymmetric Baylis-Hillman-type reaction.[51] The boron dienolate was formed upon treatment of **133** with KHMDS, followed by transmetalation of the potassium dienolate upon addition of B-bromocatechol borane **134**. Addition of an aldehyde to the reaction flask gave the corresponding α-vinyl-β-hydroxy esters **135** as single diastereoisomers in 61–78% yield (5 examples). Methanolysis of **135** using LiOMe was followed by treatment with DBU, which effected isomerisation of the double bond into conjugation with the ester, furnishing the corresponding α-ethylidene-β-hydroxy esters **137** in ≥92:8 dr [(E):(Z) ratio] and >98% ee (Scheme 24).



Scheme 24 Boron dienolate reaction. A formal asymmetric Baylis-Hillman reaction.

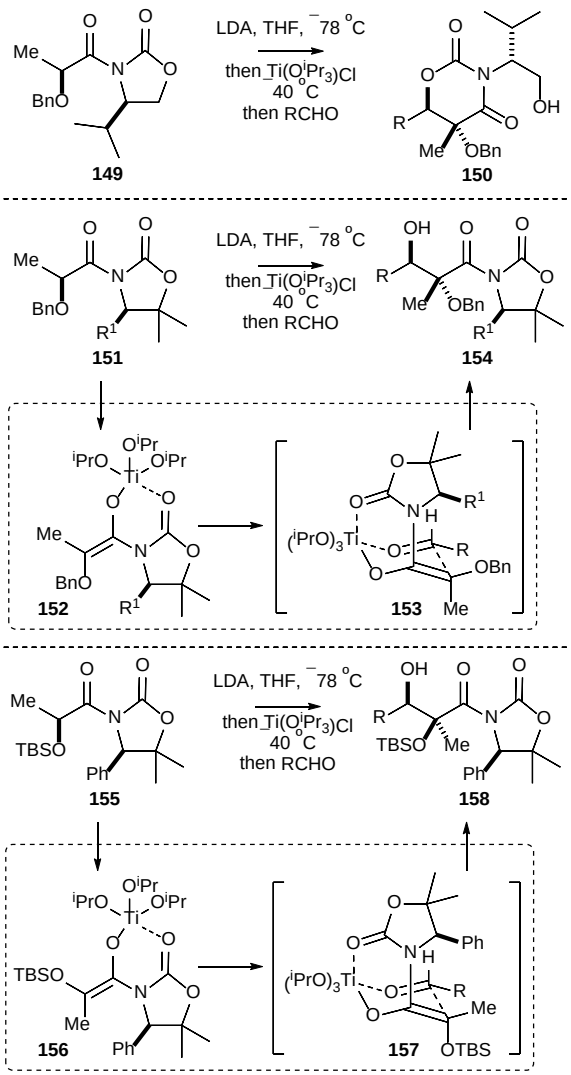
Such dienolate aldol reactions have been employed in natural product syntheses. Fukuyama et al. presented a synthesis of lysergic acid **148** which proceeded via reductive amination involving amine **145** and aldehyde equivalent **146**; both of these fragments were synthesized via titanium dienolate aldol reactions of L-Phe *N*-crotonoyl SuperQuat

138.[52] Treatment of **138** with aldehyde **139** in the presence of $TiCl_4$ and $^iPr_2NEt$ gave **141** as the only diastereoisomer in 82% yield. Hydrazinolysis gave hydrazide **143** in 94% yield and further manipulation gave the amine **145**. Meanwhile, titanium dienolate aldol reaction of **138** with aldehyde **140** gave **142** in 78% yield. O-Silyl protection of the secondary alcohol was followed by treatment with DIBAL-H to give the stable and isolable hemiaminal **146** in 63% yield. Condensation of **145** and **146** in the presence of $NaBH_3CN$ followed by *N*-Boc protection gave **147** in 60% yield. Conversion of **147** (comprising the A and B rings of the tetracyclic target) to lysergic acid **148** was then achieved in a further 13 steps, the key features of which were a ring-closing metathesis reaction (to close the D ring), a Heck reaction (to close the C ring), and oxidative cleavage of a 1,2-diol to reveal the carboxylic acid functionality (Scheme 25).[53]



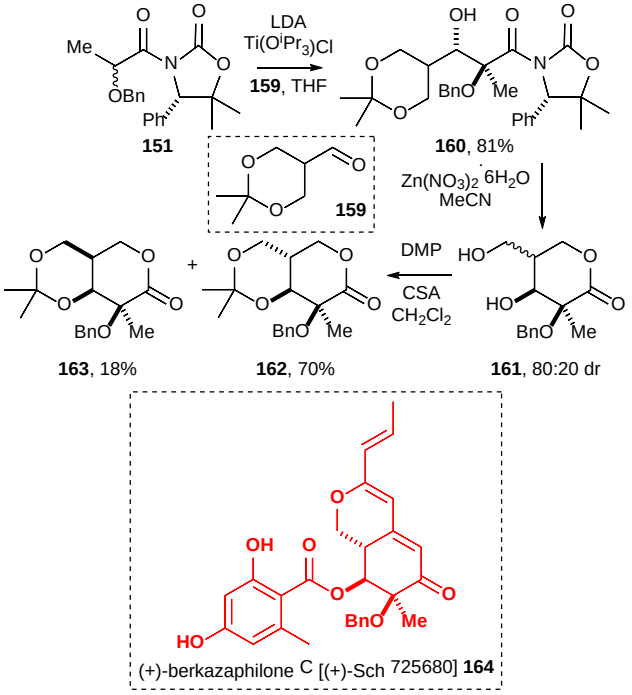
Scheme 25 Dienolate aldol reactions in the synthesis of lysergic acid **147**.

Formation of a Tertiary Alcohol at the α-Carbon. Kobayashi *et al.* pioneered the use of O-protected *N*-α-hydroxypropanoyl oxazolidin-2-one derivatives as chiral lactate equivalents in aldol reactions.[54,55] Initial studies employed reaction of L-Val Evans derivative **149** with crotonaldehyde [R = (*E*)-MeCH=CH] as a model system. Conditions for aldol reaction using a boron enolate (treatment with Bu_2BOTf and $^iPr_2NEt$, then crotonaldehyde) did not promote reaction. However, after optimisation it was found that transmetallation of the lithium enolate (formed upon treatment of **149** with LDA) to the corresponding titanium enolate upon addition of $Ti(O^iPr)_3Cl$ to the reaction flask, resulted in highly diastereoselective aldol reaction (>20:1 dr) although this was followed by cyclisation onto the endocyclic carbonyl group of the chiral auxiliary to give the 1,3-oxazinane-2,4-dione **150** [R = (*E*)-MeCH=CH], which required forcing conditions for its hydrolysis and precluded the potential for recovery of the chiral auxiliary in this case. In comparison, under identical conditions the corresponding L-Val SuperQuat derivative **151** (R^1 = ^{i}Pr) gave the aldol product **154** [R = (*E*)-MeCH=CH] in 11:1 dr, with no evidence of competitive cyclisation. This is consistent with the design features of the L-Val SuperQuat auxiliary **23**, incorporated into **151**, obviating the problem of cyclisation of the hydroxyl functionality of **154** onto the endocyclic carbonyl group. Further investigations established that reaction of L-Phg SuperQuat derivative **151** (R^1 = Ph) proceeded with superior levels of diastereoselectivity to give the corresponding adducts **154** [e.g., R = (*E*)-MeCH=CH, 24:1 dr; R = ^{i}Bu, >99:1 dr]. Finally, reaction of O-TBS protected **156** gave opposing diastereoselectivity for formation of the α-stereocentre, furnishing **158** (R = ^{i}Bu) in 17:1 dr. Enolate trapping experiments revealed the preferential formation of the corresponding (*E*)-enolate in the case of **151** and the (Z)-enolate in the case of **155**. As the vacant co-ordination site on the titanium atom within the chelated enolate conformers **152** and **156** can be taken by the aldehydic carbonyl group, these conformers represent the reactive ones in these cases, and the diastereoselectivity can thus be rationalised by invoking reaction proceeding on the sterically least encumbered face of these conformers via Zimmerman-Traxler-type transition states **153** and **157** (Scheme 26).



Scheme 26 Aldol reactions of *N*-acyl oxazolidin-2-one enolates **149**, **151** and **155** (represented in the same enantiomeric series for ease of comparison).

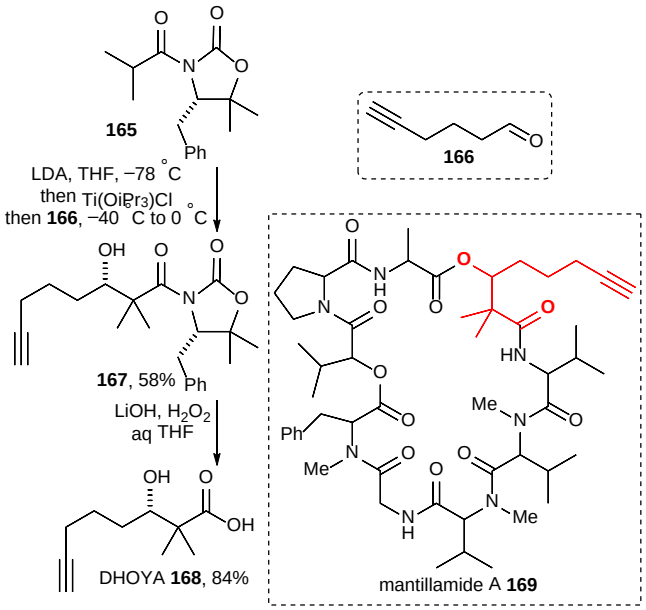
This method has subsequently been used in several target syntheses. For example, Sugawara *et al.* used it to build the quaternary stereocentre within berkazaphilone C [(+)-Sch 725680] **164**.[56] Reaction of **151**[57] with aldehyde **159** gave aldol product **160** in 81% yield. Removal of the acetonide group from **160** promoted by zinc nitrate resulted in intramolecular alcoholysis (lactonisation) to release the SuperQuat auxiliary, delivering **161** as an 80:20 mixture of epimers, although subsequent acetonide protection enabled separation, with the major diastereoisomer **162** being isolated in 70% yield (2 steps) and the minor diastereoisomer **163** in 18% yield (2 steps). Both **162** and **163** were subsequently converged on a common intermediate en route to **164** (Scheme 27).[58]



Scheme 27 Synthesis of berkazaphilone C **164**.

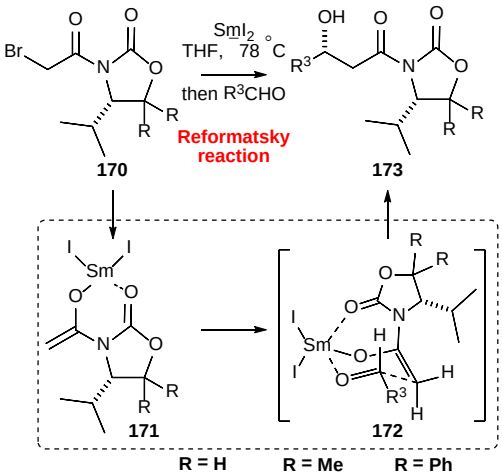
Stereoinduction at the β'-Carbon

Formation of a Quaternary (Non-Stereogenic) Centre at the α-Carbon. If an *N*-acyl SuperQuat derivative bearing two identical α-alkyl groups is exposed to the conditions developed for reaction of the corresponding O-protected *N*-α-hydroxypropanoyl derivatives **151** and **155**, then a quaternary (non-stereogenic) centre is produced at the α-carbon of the aldol product. Gerwick *et al.* reported a synthesis of 2,2-dimethyl-3-hydroxyoctynoic acid (DHOYA) **168**,[59] which is found as a sub-structural unit within a range of secondary metabolites (e.g., mantillamide A **169**). Sequential treatment of **163** with LDA, Ti(O^{i}Pr$_3$)Cl and then 5-hexynal **166** gave the corresponding aldol adduct **167** as a single diastereoisomer in 58% yield. Hydrolytic cleavage from the SuperQuat auxiliary using LiOOH gave DHOYA **168** in 84% yield. Through this study, Gerwick *et al.* were able to assign the (*R*)-configuration to the DHOYA residue present in mantillamide A **169**, and the configurations of other fragments encountered in a range of natural products[59] (Scheme 28).



Scheme 28 Synthesis of DHOYA **168**.

Reformatsky Reaction. Fukuzawa *et al.* have demonstrated a diastereoselective Reformatsky reaction mediated by samarium(II); this can be thought of as an alternative to an acrylate aldol reaction.[60] In this reaction manifold, reaction of substrates **170** incorporating geminally C(5)-disubstituted auxiliaries (R = Me or Ph) generally offered superior levels of diastereoselectivity as compared to their Evans counterparts (R = H). The diastereoselectivity in this system can be rationalised by invoking initial reduction of **170** to give the samarium(III) enolate in which the metal centre is able to co-ordinate the aldehyde and thus the reactive conformer is chelated **171**; reaction on the least hindered face of the enolate in this conformation proceeds via a Zimmerman-Traxler-type transition state **172** (analogous to **153** and **157**) to give the major diastereoisomeric product **173** (Scheme 29).



R^3	R = H yield (de) %	R = Me yield (de) %	R = Ph yield (de) %
^{i}Pr	92 (83)	64 (98)	32 (90)
^{t}Bu	87 (>99)	66 (>96)	60 (99)
n-C_7H_{15}	81 (82)	55 (94)	42 (70)
Ph	67 (64)	87 (49)	32 (>99)

Scheme 29 Asymmetric Reformatsky reaction.

Conclusions

The Evans 4-substituted oxazolidin-2-one family of chiral auxiliaries has proven to be a useful tool in asymmetric synthesis since their introduction in the 1980s. However, these auxiliaries have some shortcomings which can be overcome by the incorporation of geminal substitution at C(5). Our SuperQuat chiral auxiliaries, incorporating geminal C(5)-dimethyl substitution within the 4-substituted oxazolidin-2-one framework, were first in class of this type of modified oxazolidin-2-one chiral auxiliary. Such geminally C(5)-disubstituted auxiliaries have demonstrated significant benefits over their Evans counterparts when used in a range of reactions, which includes superior reaction diastereoselectivity, an expanded repertoire for cleavage, and ease of recycling. Since our introduction of the parent class of these auxiliaries in 1995, they have found a wide range of utility for the preparation of enantiomerically pure targets, with new applications being continually reported.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 D. A. Evans, J. Bartroli and T. L. Shih, *J. Am. Chem. Soc.*, 1981, **103**, 2127–2129.
2 D. J. Ager, I. Prakash and D. R. Schaad, *Aldrichimica Acta*, 1997, **30**, 3–12.
3 M. M. Heravi and V. Zadsirjan, *Tetrahedron: Asymmetry*, 2013, **24**, 1149–1188
4 M. M. Heravi, V. Zadsirjan and B. Farajpour, *RSC Adv.*, 2016, **6**, 30498–30551.
5 D. A. Evans, K. T. Chapman and J. Bisaha, *J. Am. Chem. Soc.*, 1988, **110**, 1238–1256 (and references cited therein).
6 S. G. Davies, H. J. Sanganee and P. Szolcsanyi, *Tetrahedron*, 1999, **55**, 3337–3354.
7 S. G. Davies and H. J. Sanganee, *Tetrahedron: Asymmetry*, 1995, **6**, 671–674.
8 S. D. Bull, S. G. Davies, S. Jones, M. E. C. Polywka, R. S. Prasad and H. J. Sanganee, *Synlett*, 1998, 519–521.
9 C. L, Gibson, K. Gillon and S. Cook, *Tetrahedron Lett.*, 1998, **39**, 6733–6736.
10 T. Hintermann and D. Seebach, *Helv. Chim. Acta*, 1998, **81**, 2093–2126.
11 M. Brenner and D. Seebach, *Helv. Chim. Acta*, 1999, **82**, 2365–2379.
12 C. Gaul and D. Seebach, *Org. Lett.*, 2000, **2**, 1501–1504.
13 C. Gaul, K. Schärer, D. Seebach, *J. Org. Chem.*, 2001, **66**, 3059–3073.
14 SuperQuat auxiliaries have found other diverse applications in synthesis which are not discussed in this review. For examples of other applications from this laboratory, see: (a) S. P. Bew, S. G. Davies and S. Fukuzawa, *Chirality*, 2000, **12**, 483–487. (b) S. G. Davies, M.-S. Key, H. Rodríguez-Solla, H. J. Sanganee, E. D. Savory and A. D. Smith, *Synlett*, 2003, 1659–1662. (c) S. G. Davies, P. M. Roberts and A. D. Smith, *Org. Biomol. Chem.*, 2007, **5**, 1405–1415. (d) C. Aciro, S. G. Davies, A. C. Garner, Y. Ishii, M.-S. Key, K. B. Ling, R. S. Prasad, P. M. Roberts, H. Rodríguez-Solla, C. O'Leary-Steele, A. J. Russell, H. J. Sanganee, E. D. Savory, A. D. Smith and J. E. Thomson, *Tetrahedron*, 2008, **64**, 9320–9344. For examples by others,

see: (e) H. Yamamoto, S. Watanabe, K. Kadotani, M. Hasegawa, M. Noguchi and S. Kanemasa, *Tetrahedron Lett.*, 2000, **41**, 3131–3136. (f) E. Marcantoni, T. Mecozzi and M. Petrini, *J. Org. Chem.*, 2002, **67**, 2989–2994. (g) A. Bueno, R. M. Moreno and A. Moyano, *Tetrahedron: Asymmetry*, 2005, **16**, 1763–1778. (h) H. Adams, R. C. Collins, S. Jones and C. J. A. Warner, *Org. Lett.*, 2011, **13**, 6576–6579. (i) P. Ivashkin, S. Couve-Bonnaire, P. Jubault and X. Pannecoucke, *Org. Lett.* 2012, **14**, 5130–5133. (j) J. Bian, D. Blakemore, J. S. Warmus, J. Sun, M. Corbett, C. R. Rose and B. M. Bechle, *Org. Lett.*, 2013, **15**, 562–565. (k) N. Sagawa, H. Sato, S. Hosokawa, *Org. Lett.*, 2017, **19**, 198–201.

15 Seebach et al. reported an analogous procedure (in detail) for preparation of 4-isopropyl-5,5-diphenyloxazolidin-2-one; see: M. Brenner, L. La Vecchia, T. Leutert and D. Seebach, *Org. Synth.*, 2003, **80**, 57–65.

16 S. G. Davies, D. A. B. Mortimer, A. W. Mulvaney, A. J. Russell, H. Skarphedinsson, A. D. Smith and R. J. Vickers, *Org. Biomol. Chem.*, 2008, **6**, 1625–1634.

17 In contrast, the corresponding SuperQuat derived from L-Ser was found to be unsuitable for attachment to solid phase; see: (a) S. P. Bew, S. D. Bull and S. G. Davies, *Tetrahedron Lett.*, 2000, **41**, 7577–7581. (b) S. P. Bew, S. D. Bull, S. G. Davies, E. D. Savory and D. J. Watkin, *Tetrahedron*, 2002, **58**, 9387–9401.

18 S. D. Bull, S. G. Davies, M.-S. Key, R. L. Nicholson and E. D. Savory, *Chem. Commun.* 2000, 1721–1722.

19 S. D. Bull, S. G. Davies, A. C. Garner, D. Kruchinin, M.-S. Key, P. M. Roberts, E. D. Savory, A. D. Smith and J. E. Thomson, *Org. Biomol. Chem.*, 2006, **4**, 2945–2964.

20 D. Schinzer, A. Bauer, O. M. Böhm, A. Limberg and M. Cordes, *Chem. Eur. J.*, 1999, **5**, 2483–2491.

21 For other examples of the utility of enolate alkylations in target syntheses, see: (a) L. Tomas, G. Boije af Gennäs, M. Aude Hiebel, P. Hampson, D. Gueyrard, B. Pelotier, J. Yli-Kauhaluoma, O. Piva, J. M. Lord, P. G. Goekjian, *Chem. Eur. J.* 2012, **18**, 7452–7466. (b) R. F. Valeev, R. F. Bikzhanov and M. S. Miftakhov, *Mendeleev Commun.*, 2014, **24**, 372–373.

22 J. Alvarado, A. T. Herrman and A. Zakarian, *J. Org. Chem.* 2014, **79**, 6206–6220.

23 P. J. Mabe and A. Zakarian, *Org. Lett.*, 2014, **16**, 516–519.

24 A. Gómez-Palomino, M. Pellicena, M.; J. Manuel Romo, R. Solà, P. Romea, F. Urpí and M. Font-Bardia, *Chem Eur. J.* 2014, **20**, 10153–10159.

25 S. Beaumont, E. A. Ilardi, L. R. Monroe and A. Zakarian, *J. Am. Chem. Soc.*, 2010, **132**, 1482–1483.

26 A. T. Herrmann, L. L. Smith and A. Zakarian, *J. Am. Chem. Soc.*, 2012, **134**, 6976–6979.

27 Z. Gu and A. Zakarian, *Angew. Chem. Int. Ed.*, 2010, **49**, 9702–9705.

28 J. E. Beddow, S. G. Davies, A. D. Smith and A. J. Russell, *Chem. Commun.*, 2004, 2778–2779.

29 J. E. Beddow, S. G. Davies, K. B. Ling, P. M. Roberts, A. J. Russell, A. D. Smith and J. E. Thomson, *Org. Biomol. Chem.*, 2007, **5**, 2812–2825.

30 S. G. Davies, J. A. Lee, P. M. Roberts, R. S. Shah and J. E. Thomson, *Chem. Commun.*, 2012, **48**, 9236–9238.

31 S. G. Davies, P. M. Roberts, R. S. Shah and J. E. Thomson, *Tetrahedron Lett.*, 2013, **54**, 6423–6426.

32 L. M. Pratt, R. P. Beckett, S. J. Davies, S. B. Launchbury, A. Miller, Z. M. Spavold, R. S. Todd and M. Whittaker, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 2585–2588.

33 S. D. Bull, S. G. Davies, R. L. Nicholson, H. J. Sanganee and A. D. Smith, *Org. Biomol. Chem.*, 2003, **1**, 2886–2899.

34 V. J. Hruby, K. C. Russell and E. Nicolas, *J. Org. Chem.* 1993, **58**, 766–770.

35 For other examples of utility of conjugate additions in target syntheses, see: (a) K. V. Lawson, T. E. Rose and P. G. Harran, *Tetrahedron Lett.*, 2011, **52**, 653–654. (b) Z. Leitis and V. Lusis, *Tetrahedron: Asymmetry*, 2016, **27**, 843–851.

36 N. Lei, Y. Rui, Z. Conghai, Y. Haichuan, Y. Shengjiao and L. Jun, *Chin. J. Chem.*, 2012, **30**, 460–465.

37 For a more detailed mechanistic study of the aldol reaction involving the corresponding enolates derived from *N*-acyl Evans auxiliaries, see: Z. Zhang and D. B. Collum, *J. Org. Chem.*, 2001, **82**, 7595–7601.

38 S. G. Davies, R. L. Nicholson and A. D. Smith, *Synlett*, 2002, 1637–1640.

39 S. G. Davies, I. A. Hunter, R. L. Nicholson, P. M. Roberts, E. D. Savory and A. D. Smith, *Tetrahedron*, 2004, **60**, 7553–7577.

40 S. G. Davies, R. L. Nicholson and A. D. Smith, *Org. Biomol. Chem.*, 2004, **2**, 3385–3400.

41 S. G. Davies, R. L. Nicholson and A. D. Smith, *Org. Biomol. Chem.*, 2005, **3**, 348–359.

42 R. Green, M. Cheeseman, S. Duffill, A. Merritt and S. D. Bull, *Tetrahedron Lett.*, 2005, **46**, 7931–7934.

43 M. F. Chellat, N. Proust, M. G. Lauer and J. P. Stambuli, *Org. Lett.*, 2011, **13**, 3246–3249.

44 For investigations delineating the nature of the "matched" and "mismatched" reaction pairings in these systems, see: Ref 40.

45 For example, see: (a) M. Cheeseman, F. J. P. Feuillet, A. L. Johnson and S. D. Bull, *Chem. Commun.*, 2005, 2372–2374. (b) M. Cheeseman, I. R. Davies, P. Axe, A. L. Johnson and S. D. Bull, *Org. Biomol. Chem.*, 2009, **7**, 3537–3548. (c) D. J. Aitken, S. D. Bull, I. R. Davies, L. Drouin, J. Ollivier and J. Peed, *Synlett*, 2010, 2729–2732.

46 M. Cheeseman and S. D. Bull, *Synlett*, 2006, 1119–1121.

47 For other examples of the utility of enolate aldol reactions in target syntheses, see: (a) E. Bourcet, F. Fache and O. Piva, *Eur. J. Org. Chem.* 2010, 4075–4087. (b) A. Nakazaki, T. Era and S. Kobayashi, *Chem. Lett.*, 2008, **37**, 770–771. (c) J. Peed, I. R. Davies, L. R. Peacock, J. E. Taylor, G. Kociok-Köhn and S. D. Bull, *J. Org. Chem.*, 2012, **77**, 543–555.

48 This procedure was established for *N*-acyl Evans oxazolidin-2-ones; see: D. A. Evans, J. S. Tedrow, J. T. Shaw and C. W. Downey, *J. Am. Chem. Soc.*, 2002, **124**, 392–393.

49 I. R. Davies, M. Cheeseman, R. Green, M. F. Mahon, A. Merritt and S. D. Bull, *Org. Lett.*, 2009, **11**, 2896–2899.

50 J. Peed, I. P. Dominguez, I. R. Davies, M. Cheeseman, J. E. Taylor and S. D. Bull, *Org. Lett.*, 2011, **13**, 3592–3595.

51 S. G. Davies, D. L. Elend, S. Jones, P. M. Roberts, E. D. Savory, A. D. Smith and J. E. Thomson, *Tetrahedron*, 2009, **65**, 7837–7851.

52 S. Umezaki, S. Yokoshima and T. Fukuyama, *Org. Lett.*, 2013, **15**, 4230–4233.

53 For other examples of the utility of dienolate aldol reactions in target syntheses, see: (a) H. Sakaguchi, H. Tokuyama and T. Fukuyama, *Org. Lett.*, 2007, **9**, 1635–1638. (b) H. Abas, S. M. Linsdall, M. Mamboury, H. S. Rzepa and A. C. Spivey, *Org. Lett.*, 2017, **19**, 2486–2489.

54 T. Kamino, Y. Murata, N. Kawai, S. Hosokawa and S. Kobayashi, *Tetrahedron Lett.*, 2001, **42**, 5249–5252.

55 Y. Murata, T. Kamino, S. Hosokawa and S. Kobayashi, *Tetrahedron Lett.*, 2002, **43**, 8121–8123.

56 T. Takeuchi, Y. Mizushina, S. Takaichi, N. Inoue, K. Kuramochi S. Shimura, Y. Myobatake, Y. Katayama, K. Takemoto, S. Endo, S. Kamisuki and F. Sugawara, *Org. Lett.*, 2012, **14**, 4303–4305.

57 The authors do not comment as to whether **150** is diastereoisomerically pure or not.

58 For other examples of the utility of this class of aldol reactions in target syntheses, see: (a) Y. Murata, T. Kamino, T. Aoki, S. Hosokawa and S. Kobayashi, *Angew. Chem. Int. Ed.*, 2004, **43**, 3175–3177. (b) M. T. Crimmins, M. Shamszad and A. E. Mattson, *Org. Lett.*, 2010, **12**, 2614–2617. (c) T.

Ohtani, S. Tsukamoto, H. Kanda, K. Misawa, Y. Urakawa, T. Fujimaki, M. Imoto, Y. Takahashi, D. Takahashi and K. Toshima, *Org. Lett.*, 2010, **12**, 5068–5071. (d) Y. Onodera, T. Suzuki and S. Kobayashi, *Org. Lett.*, 2011, **13**, 50–53. (e) B. V. D. Vijaykumar, P. Mallesham and S. Chandrasekhar, *Eur. J. Org. Chem.*, 2012, 988–994. (f) J. S. Warmus, C. L. Quinn, C. Taylor, S. T. Murphy, T. A. Johnson, C. Limberakis, D. Ortwine, J. Bronstein, P. Pagano, J. D. Knafels, S. Lightle, I. Mochalkin, R. Brideau and T. Podoll, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 2536–2543. (g) T. Suzuki, M. Fujimura, K. Fujita and S. Kobayashi, *Tetrahedron*, 2017, **73**, 3652–3659.

59 (a) M. Taniguchi, J. K. Nunnery, N. Engene, E. Esquenazi, T. Byrum, P. C. Dorrestein and W. H. Gerwick, *J. Nat. Prod.*, 2010, **73**, 393–398. (b) J. K. Nunnery, T. L. Suyama, R. G. Linigton and W. H. Gerwick, *Tetrahedron Lett.*, 2011, **52**, 2929–2932.

60 S. Fukuzawa, H. Matsuzawa and S. Yoshimitsu, *J. Org. Chem.*, 2000, **65**, 1702–1706.