

## Double asymmetric induction as a mechanistic probe: conjugate addition for the asymmetric synthesis of a pseudotriptide

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Double asymmetric induction as a mechanistic probe indicates that, for the conjugate addition of (*R*)- and (*S*)-lithium *N*-benzyl-*N*- $\alpha$ -methylbenzylamide to (*S*)-3'-phenylprop-2'-enoyl-4-benzylloxazolidinone, the reactive conformation of the *N*-acyl oxazolidinone is the *anti-s-cis* form, facilitating the asymmetric synthesis of a pseudotriptide.

The conjugate addition of nucleophiles to  $\alpha,\beta$ -unsaturated carbonyl compounds plays a fundamental role in the stereoselective formation of  $\beta$ -functionalised carbonyl components. Stereochemical control in these reactions is typically achieved by the use of chiral auxiliaries,<sup>1</sup> or chiral catalysts,<sup>2</sup> with the diastereoselective conjugate addition of nucleophiles to *N*-enoyl derivatives of oxazolidinones being used extensively.<sup>3</sup> In these reactions, it is possible for an (*E*)- $\alpha,\beta$ -unsaturated oxazolidinone component to undergo diastereoselective 1,4-addition via any of the four possible *syn*- or *anti*-, and *s-cis* or *s-trans* conformations 1–4 (Fig. 1).<sup>4</sup> An intriguing mechanistic dichotomy exists, since the same face selectivity on either the *syn-s-cis* or the *anti-s-trans* conformations leads to the same stereochemical result, as with the *syn-s-trans* or the *anti-s-cis* pair. In these systems, it has been proposed that the diastereoselective conjugate addition of organocuprates occurs via the Lewis acid chelated *syn-s-cis* conformation,<sup>5</sup> with the diastereoselectivity postulated to reflect the populations of the reactive conformers of these substrates.<sup>6,7</sup> As lithium amides are widely recognised to add in a conjugate fashion to (*E*)- $\alpha,\beta$ -unsaturated acceptors in the *s-cis* conformation,<sup>8</sup> the reaction of lithium amides and *N*-enoyl oxazolidinones may be used as a mechanistic probe; we communicate herein a novel strategy employing double asymmetric induction to determine the reactive conformation of the oxazolidinone in this manifold.

Given the known preference for lithium amides to react with (*E*)- $\alpha,\beta$ -unsaturated acceptors exclusively in the *s-cis* conformation,<sup>8</sup> conjugate addition to an (*E*)-*N*-enoyl oxazolidinone may occur only via either the *syn*- or *anti-s-cis* conformations 1 and 2 respectively.<sup>9</sup> Addition of lithium dibenzylamide to (*S*)-*N*-3'-phenylprop-2'-enoyl-4-benzylloxazolidinone 5 furnished a 79 : 21 mixture of diastereoisomers (58% d.e.) in 91% combined yield, with purification of the major diastereoisomer (4*S*,3'*R*)-6 by fractional crystallisation facilitating its isolation in 53% yield and >98% d.e. The configuration at C(3') within  $\beta$ -amino ester (4*S*,3'*R*)-6 was confirmed by deprotection via hydrolysis and hydrogenolysis, giving (*R*)- $\beta$ -phenylalanine 7 {[ $\alpha$ ]<sub>D</sub><sup>22</sup> +6.2 (c 0.6, H<sub>2</sub>O), lit.<sup>10</sup> [ $\alpha$ ]<sub>D</sub><sup>19</sup> +6.5 (c 1.0, H<sub>2</sub>O)} after purification by ion exchange chromatography (Scheme 1).

On the reasonable assumption that addition of lithium dibenzylamide occurs *anti* to the benzyl stereodirecting group of the

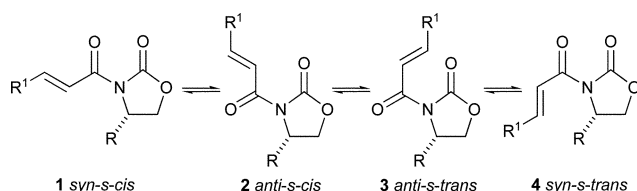
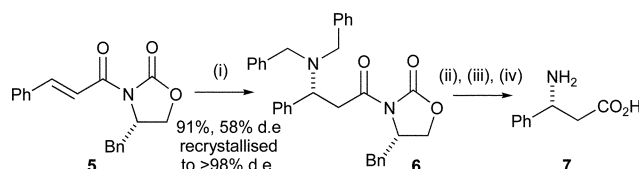


Fig. 1 Possible conformations of (*E*)-*N*-enoyl oxazolidinones for conjugate addition.



Scheme 1 Reagents and conditions: (i) Lithium dibenzylamide (1.6 eq), THF,  $-78\text{ }^{\circ}\text{C}$ ; (ii) LiOH, H<sub>2</sub>O<sub>2</sub>, THF : H<sub>2</sub>O (3 : 1),  $0\text{ }^{\circ}\text{C}$  to rt; (iii) MeOH : H<sub>2</sub>O : AcOH (40 : 4 : 1), Pd(OH)<sub>2</sub> on C, H<sub>2</sub> (1 atm); (iv) 1 M HCl then Dowex 50W-8 ion exchange chromatography.

oxazolidinone,<sup>5</sup> the low diastereoselectivity observed in this protocol is compatible with a number of mechanistic scenarios. Addition of lithium dibenzylamide may occur (i) with high facial selectivity to a unequilibrating 79 : 21 mixture of *anti-s-cis* to *syn-s-cis* conformers of (*S*)-5; (ii) with moderate (79 : 21) facial selectivity via exclusive addition to the *anti-s-cis* conformation of (*S*)-5; (iii) to a 58 : 42 mixture of *anti*- to *syn-s-cis* conformers, with complete facial selectivity for addition to the *anti-s-cis* conformer but with zero selectivity to the *syn-s-cis* conformer; (iv) to a rapidly equilibrating mixture of *anti-s-cis* to *syn-s-cis* conformers with unknown facial control. To distinguish between these alternate reaction manifolds, the conjugate additions of lithium (*R*)- and (*S*)-*N*-benzyl-*N*- $\alpha$ -methylbenzylamide 8 to (*S*)-5 were deployed, as the observation of double asymmetric induction, combined with the sense of the matched and mismatched pairings, should determine the reactive conformation of the acceptor. Conjugate addition of lithium amide (*R*)-8 to acceptor (*S*)-5 gave an inseparable mixture of diastereoisomers with low diastereoselectivity (66% d.e.),<sup>11</sup> furnishing (4*S*,3'*S*, $\alpha$ *R*)-9 in 83% isolated yield and 66% d.e. after chromatographic purification. However, conjugate addition of lithium amide (*S*)-8 to (*S*)-5 gave (4*S*,3'*R*, $\alpha$ *S*)-10 in >98% d.e.<sup>11</sup> and in 84% isolated yield after crystallisation from the crude reaction mixture (Fig. 2). The (4*S*,3'*S*, $\alpha$ *R*)- and (4*S*,3'*R*, $\alpha$ *S*)-configurations within 9 and 10 from the mismatched and matched reactions respectively were confirmed unambiguously by a separate chemical synthesis in each case, with the sense of asymmetric induction consistent with the stereocontrol of the chiral lithium amide, not the oxazolidinone, dominating the reaction selectivity.<sup>12</sup> Conjugate additions of lithium amides (*R*)-8 and (*S*)-8 in the presence of chelating components such as LiBr, MeMgBr, Ti(Oi-

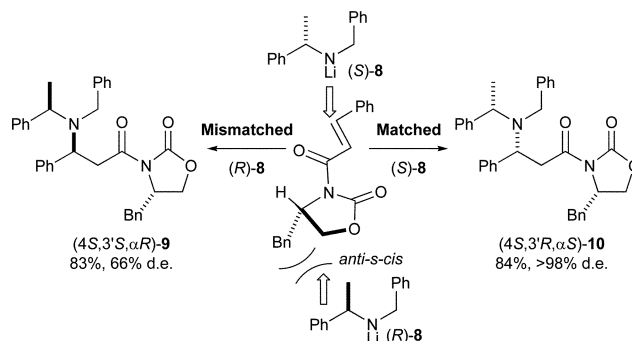


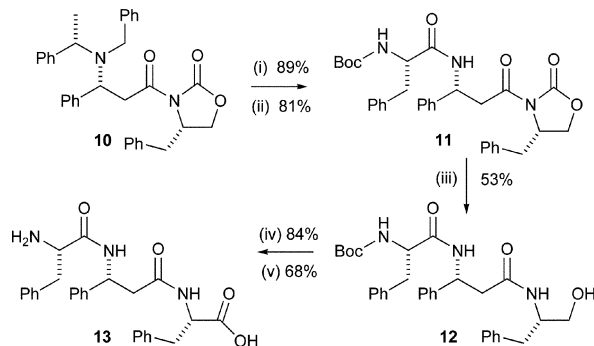
Fig. 2 Model to rationalise the observed matched and mismatched double asymmetric induction.

Pr<sub>3</sub>Cl and Zn(OTf)<sub>2</sub>, in which the carbonyl groups of the *N*-enoyl oxazolidinone may be expected to be held in the *syn* conformation,<sup>5</sup> were next investigated. Upon addition of lithium amides (*R*)-**8** and (*S*)-**8** to (*S*)-**5** in the presence of these additives, the observed level of diastereoselectivity remained unchanged (66% d.e. and >98% d.e. respectively), although 70–90% of the starting material was recovered, even upon extended reaction times.

The observation of matched and mismatched double asymmetric induction in these reactions rules out the reaction proceeding under Curtin–Hammett control {scenario (iv)}, as in this mechanistic scheme conjugate addition of both (*R*)-**8** and (*S*)-**8** to *syn-s-cis* and *anti-s-cis* (*S*)-**5** respectively would be matched, and proceed with equal and high diastereocontrol. If the reaction proceeds under hypothesis (i), a mixture of matched {(*R*), *syn* and (*S*), *anti*} and mismatched {(*S*), *syn* and (*R*), *anti*} reactions would be observed, so in neither case would a high d.e. be expected. For case (iii), assuming the addition of a Lewis acid alters the ratio of *syn* : *anti* conformers, a change in the level of diastereoselectivity upon addition of both lithium amides (*R*)-**8** and (*S*)-**8** would be observed. In this way, the observed results can only be consistent with scenario (ii). In the matched case, addition of lithium amide (*S*)-**8** to acceptor **5** in the *anti-s-cis* conformation results in the preferential formation of (4*S*,3'*R*, $\alpha$ *S*)-**10** with high diastereoselectivity. In the mismatched case, addition of lithium amide (*R*)-**8** to acceptor **5** in the *anti-s-cis* conformation results in the preferential formation of (4*S*,3'*S*, $\alpha$ *R*)-**9** with reduced levels of diastereoselectivity (Fig. 2). Furthermore, the lower conversions but unchanged stereoselectivities upon addition of (*R*)-**8** and (*S*)-**8** to (*S*)-**5** in the presence of Lewis acids is consistent with the *syn-s-cis* conformation being unreactive.

The synthetic utility of this double asymmetric induction protocol was then demonstrated. Although homo-oligomers of both  $\alpha$ - and  $\beta$ -amino acid derivatives are known to show secondary structural characteristics, we are interested in the preparation and structural characterisation of 'mixed' oligomers containing both  $\alpha$ - and  $\beta$ -amino acids.<sup>13</sup>  $\beta$ -Amino ester (4*S*,3'*S*, $\alpha$ *R*)-**10** was envisaged as part of a novel asymmetric approach towards the preparation of a pseudotriptide derived from  $\alpha$ - and  $\beta$ -amino acids. In this strategy, the protected functionality within the oxazolidinone chiral auxiliary was to be unmasked as a latent  $\alpha$ -amino acid *via* endocyclic cleavage of the auxiliary, a process that typically predominates under standard hydrolysis conditions with either bulky  $\alpha$ -substituted or  $\beta$ -heteroatom derivatives of oxazolidinones.<sup>14,15</sup> Hydrogenolysis of tertiary  $\beta$ -amino ester **10** to the primary amine and subsequent coupling with *N*-Boc-Phe gave pseudopeptide **11**, which gave alcohol **12** upon treatment with LiOH. Oxidation of **12** to the acid with Jones reagent followed by *N*-Boc deprotection furnished the pseudopeptide  $\alpha,\beta,\alpha$ -tri(phenylalanine) **13** (Scheme 2).

In conclusion, double asymmetric induction in the reaction between homochiral lithium *N*-benzyl-*N*- $\alpha$ -methylbenzylamide and *N*-enoyl oxazolidinone **5** demonstrates that the conjugate addition reaction occurs *via* the *anti-s-cis* conformation. The



**Scheme 2** Reagents and conditions: (i) Pd(OH)<sub>2</sub> on C, AcOH, H<sub>2</sub> (5 atm), rt; (ii) Boc-Phe, DCC, THF, 0 °C; (iii) LiOH (4.8 eq), THF : H<sub>2</sub>O (2 : 1), rt; (iv) CrO<sub>3</sub>, H<sub>2</sub>SO<sub>4</sub>, acetone, 0 °C; (v) TFA : DCM (1 : 1), rt then purification on reverse phase RP-18 gel.

potential of this methodology for the efficient asymmetric synthesis of a novel  $\alpha$ - and  $\beta$ -amino acid containing pseudotriptide acid has been demonstrated. By systematic variation of the  $\alpha$ -amino acid components and  $\beta$ -substitution of the  $\alpha,\beta$ -unsaturated acceptor, this methodology should allow access to a vast number of unnatural oligomers with bespoke substitution patterns on the peptide backbone. Further application of double asymmetric induction as a mechanistic tool, and the application of this methodology for the synthesis of a range of pseudopeptides is currently underway in our laboratory.

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