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Conformational control in the SuperQuat chiral auxiliary 5,5-dimethyl-4-*iso*-propyloxazolidin-2-one induces the *iso*-propyl group to mimic a *tert*-butyl group

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^{1}H NMR nOe spectroscopic studies reveal that conformational control in the enolates of *N*-acyl-5,5-dimethyl-4-*iso*-propyloxazolidin-2-ones ensures that the stereodirecting effect of its 4-*iso*-propyl-5,5-dimethyl functional group affords superior levels of facial selectivity normally associated with enolates derived from *N*-acyl-4-*tert*-butyloxazolidin-2-ones.

The versatile oxazolidin-2-one based chiral auxiliary methodology first developed by Evans *et al.* has been widely used for the asymmetric synthesis of homochiral α-substituted carboxylic acids.[1] L-Valine derived 4-*iso*-propyloxazolidin-2-one **1a** is normally employed to control the asymmetric alkylation of enolates derived from the corresponding *N*-acyloxazolidin-2-ones, however it is known that the *tert*-leucine derived 4-*tert*-butyloxazolidin-2-one **1b** affords superior diastereoselectivities for this class of enolate alkylation. Thus, while methylation of the enolate of (*S*)-*N*-butyryl-4-*iso*-propyloxazolidin-2-one **2a** affords (4*S*,2′*S*)-**3a** in 82% de, methylation of the corresponding (*S*)-*N*-butyryl-4-*tert*-butyloxazolidin-2-one **2b** affords (4*S*,2′*S*)-**3b** in 97% de (Scheme 1).[2] However, the parent non-proteinogenic α-amino acid (*S*)-*tert*-leucine, from which **1b** is derived, is prohibitively expensive.[3]

We have recently reported on the development of a new family of SuperQuat 5,5-dimethyl-4-alkyloxazolidin-2-ones for asymmetric synthesis which fully address the troublesome endocyclic cleavage pathway associated with alkaline hydrolysis of *N*-acyloxazolidin-2-ones.[4] Whilst the primary function of the C(5)-*gem*-dimethyl group within *N*-acyl-5,5-dimethyl-4-alkyloxazolidin-2-ones is to completely suppress the endocyclic cleavage pathway, it was proposed on the basis of molecular modelling calculations (Fig. 1)[4] that the presence of this functionality might also serve a secondary function by enhancing the observed diastereofacial selectivity during enolate alkylation.[5,6]

As a consequence of this conformational preference, it was predicted that the facial selectivity observed for alkylation of 5,5-dimethyl-4-*iso*-propyl enolate **5c** would be significantly higher than that observed for alkylation of the corresponding enolate **5a** derived from 4-*iso*-propyloxazolidin-2-one **1a**. It follows therefore in terms of enolate alkylation that the *iso*-propyl group of the SuperQuat oxazolidin-2-ones mimics a *tert*-butyl group. In order to investigate this hypothesis, competitive enolate alkylations were carried out on the three enolates **5a**–**c** under identical conditions, *via* deprotonation of the corresponding *N*-acyloxazolidin-2-ones **4a**–**c** in THF at −78 °C, followed by warming to 0 °C, and addition of 1.1 equiv. MeI. These studies revealed that the diastereoselectivity for alkylation of enolate **5a** {(92% (4*S*,2′*S*)-**6a**: 8% (4*S*,2′*R*)-**7a**); 84% de} was significantly lower than that observed for both enolate **5b** {(98.5% (4*S*,2′*S*)-**6b**: 1.5% (4*S*,2′*R*)-**7b**); 97% de} and enolate **5c** {(97% (4*S*,2′*S*)-**6c**: 3% (4*S*,2′*R*)-**7c**); 94% de} (Scheme 2). These enolate alkylation reactions were then repeated under more precisely controlled conditions by carrying out the enolate methylation reactions on a 1:1 mixture of (*S*)-4-*iso*-propyl enolate **5a** and (*S*)-5,5-dimethyl-4-*iso*-propyl enolate **5c**, and a 1:1 mixture of (*S*)-4-*tert*-butyl enolate **5b** and enolate **5c**, in the same reaction vessel. These direct comparison studies reveal an identical trend to the separate enolate studies affording diastereoselectivities for (*S*)-4-*tert*-butyl enolate **5b** (97% de) > (*S*)-5,5-dimethyl-4-*iso*-propyl enolate **5c** (94% de) > (*S*)-4-*iso*-

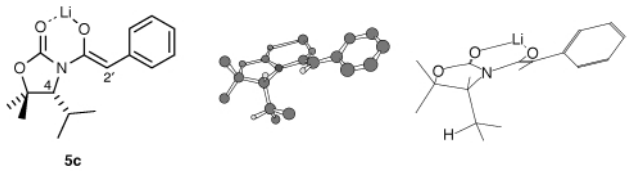
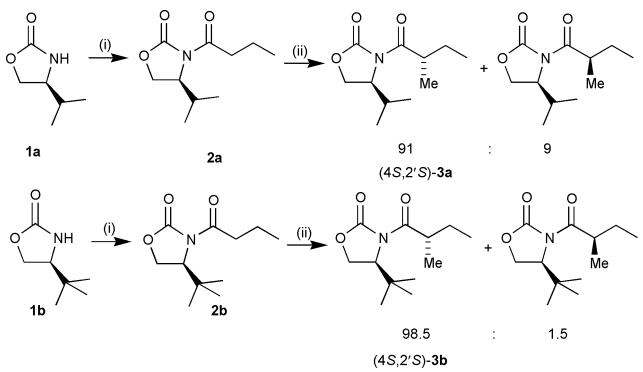
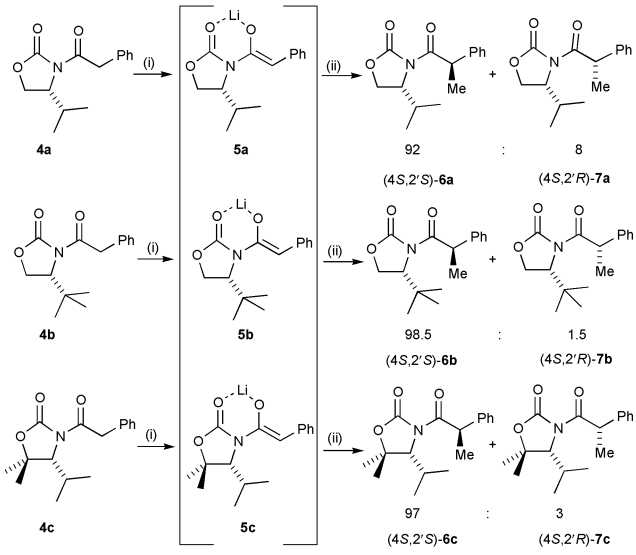


Fig. 1 Energy minimisation of SuperQuat enolate **5c** using MOPAC with an MM2 force field.



Scheme 1 *Reagents and conditions:* (i) *n*-BuLi, butyryl chloride, THF, −78 °C; (ii) LDA, MeI, THF, −30 °C.



Scheme 2 *Reagents and conditions:* (i) LHMDS, THF, −78 to 0 °C; (ii) 1.1 equiv. MeI.

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propyl enolate **5a** (84% de). The diastereoselectivities for all of the enolate alkylation reactions investigated were calculated from integration of the resonances corresponding to both the major (4*S*,2′*S*)-diastereoisomers **6a**–**c** and minor (4*S*,2′*R*)-diastereoisomers **7a**–**c** in the ^{1}H NMR spectrum of each crude reaction mixture. Authentic pure samples of both the major (4*S*,2′*S*)-diastereoisomers **6a**–**c** and minor (4*S*,2′*R*)-diastereoisomers **7a**–**c** were obtained *via* chromatographic purification of the three pairs of diastereoisomers **6a**–**c** and **7a**–**c** obtained from *N*-acylation of the lithium anions of each of the parent oxazolidin-2-ones with racemic 2-phenylpropanoyl chloride, and fully characterised.

Having clearly demonstrated that methylation of the 5,5-dimethyl-4-*iso*-propyl enolate **5c** with MeI at 0 °C occurred in higher de than methylation of the corresponding 4-*iso*-propyl enolate **5a**, ^{1}H nOe NMR spectroscopic analysis on the enolates **5a** and **5c** was carried out in order to probe directly their conformation in solution. Enolates **5a** and **5c** were generated *via* treatment of **4a** and **4c** with 1 equiv. of LHMDS at −78 °C in d_8-THF, followed by warming the resulting solution to 0 °C. The ^{1}H NMR spectra of both **5a** and **5c** were entirely consistent with the proposed (*Z*)-enolate structures since enolate **5a** showed a singlet resonance at δ 4.58, while enolate **5c** exhibited a singlet resonance at δ 4.68, corresponding to the C(2′) vinylic proton of the enolate functionality in each case. Examination of the resonances corresponding to the *iso*-propyl C*H*(Me)$_2$ protons in the ^{1}H NMR spectrum of enolates **5a** and **5c** revealed small vicinal coupling constants of 3.2 and 2.3 Hz respectively between the *iso*-propyl C*H*(Me)$_2$ proton and the oxazolidin-2-one H(4) proton. This is consistent with both enolates **5a** and **5c** adopting conformations in which the C*H*(Me)$_2$ protons of their *iso*-propyl groups lie approximately syn- or anti-periplanar to the C(4)–C(5) bond of the oxazolidin-2-one ring, with both methyl groups of their *iso*-propyl units directed either towards, or away from the attached enolate fragment. Qualitative ^{1}H nOe NMR spectroscopic analysis of the 4-*iso*-propyl enolate **5a** in d_8-THF at 0 °C revealed a strong enhancement between the C(2′) vinylic proton of the enolate fragment and the oxazolidin-2-one *iso*-propyl C*H*(Me)$_2$ proton, with no nOe enhancement with either of the *iso*-propyl CH(C*H*$_3$)$_2$ groups. Further strong nOe enhancements were observed between the *pro*-(*S*) H(5) proton and both of the *iso*-propyl CH(C*H*$_3$)$_2$ methyl groups. These nOe enhancements are consistent with a major enolate conformer **5a** in which both of the *iso*-propyl methyl groups are directed away from the attached enolate fragment (Fig. 2). In contrast, qualitative ^{1}H nOe NMR spectroscopic analysis of enolate **5c** revealed both a medium and small enhancement between the C(2′) vinylic proton of the enolate fragment and each of the methyl groups of the *iso*-propyl CH(C*H*$_3$)$_2$ group. A further strong nOe enhancement was observed between the C*H*(Me)$_2$ proton and one of the C(5)-*gem*-dimethyl groups. These nOe enhancements are consistent with the proposed model for 5,5-dimethyl-4-*iso*-propyl enolate **5c** in which the major conformer in solution has both methyl groups of the stereocontrolling *iso*-propyl group directed towards the attached enolate fragment (Fig. 3). Importantly, both samples of enolates **5a** and **5c** in d_8-THF at 0 °C used in these ^{1}H NMR

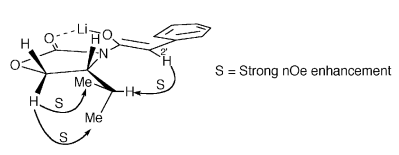


Fig. 2 nOe study on Evans' enolate **5a**. Other nOe enhancements omitted for clarity.

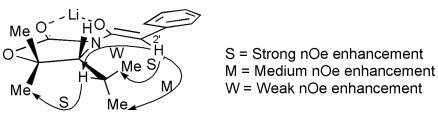
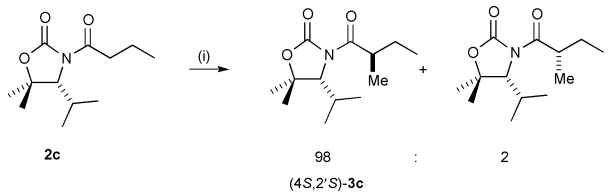


Fig. 3 nOe study on SuperQuat enolate **5c**. Other nOe enhancements omitted for clarity.



Scheme 3 *Reagents and conditions:* (i) LDA, MeI, THF, −30 °C.

studies were shown to be stable over the period of the experiment *via* subsequent treatment of both solutions of enolates **5a** and **5c** with MeI to afford the major diastereoisomers **6a** and **6c** with diastereoselectivites identical to those obtained previously.

In order to confirm the enhanced facial selectivity observed for alkylation of *N*-acyl-5,5-dimethyl-4-*iso*-propyl enolates, methylation of the enolate of *N*-butyryl-5,5-dimethyl-4-*iso*-propyloxazolidin-2-one **2c** was carried out under the original conditions described by Evans *et al.* for *N*-butyryloxazolidin-2-ones **2a** and **2b**. Thus, methylation of the enolate of **2c** gave the major diastereoisomer (4*S*,2′*S*)-**3c** in 96% de (Scheme 3), which is significantly higher than that obtained for methylation of the enolate of *N*-butyryl-4-*iso*-propyloxazolidin-2-one **3a** of 82% de, and compares favourably with that observed for methylation of the enolate of *N*-butyryl-4-*tert*-butyryloxazolidin-2-one **3b** of 97% de.

In conclusion, ^{1}H NMR nOe spectroscopic studies confirm that the superior enolate alkylation diastereoselectivities observed for (*S*)-5,5-dimethyl-4-*iso*-propyl enolate **5c** over (*S*)-4-*iso*-propyl enolate **5a** is a result of steric interactions between the C(5)-*gem*-dimethyl and the *iso*-propyl group of **5c** which direct both methyl groups of the *iso*-propyl stereocontrolling group towards the enolate fragment. We believe that the strategy outlined above of employing adjacent *gem*-dimethyl groups to control the conformation of an *iso*-propyl group such that it mimics a *tert*-butyl group is a general one, and we are currently investigating the development of a wide range of novel ligands and auxiliaries containing this structural motif, which is easily prepared from valine, as replacements for the corresponding *tert*-leucine derived analogues.[7]

We thank Dr Barbara Odell for her technical assistance with the qualitative ^{1}H nOe NMR spectroscopic studies on enolates **5a** and **5c**.

Notes and references

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