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Chiral relay effects influence the facial selectivity of *N*-alkylated 5-phenylmorpholin-2-one enolates

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Abstract

Alkylation studies on the enolate of *N*-methyl morpholinone **7** clearly reveal that the observed *cis*-selectivity is consistent with a chiral relay system operating to invert the stereochemical information of the auxiliary's C_5 stereogenic centre.

We have recently reported on a new chiral relay auxiliary for the asymmetric synthesis of α-amino acids which relies on the use of achiral *N,N'-p*-methoxybenzyl protecting groups to enhance stereoselectivity during alkylation of enolate **1** (Fig. 1).[1] A survey of the literature revealed that this type of chiral relay system, where non-stereogenic protecting groups serve to both relay and amplify the stereochemical information of an existing stereocentre, could be responsible for the anomalous results observed during alkylation of the enolates of (*R*)-5-phenylmorpholin-2-one based chiral auxiliaries.[2] Alkylation of the enolate of *N*-Boc-(*R*)-5-phenylmorpholin-2-one **2** with benzyl bromide affords *trans*-benzylated auxiliary **3** in >99% d.e., while a similar alkylation of the enolate of the corresponding *N*-benzylated auxiliary **4** gave the opposing *cis*-benzylated product **5** in 89% d.e.[2] (Scheme 1).

The *trans*-selectivity observed for alkylation of the enolate of **2** is readily explained by invoking a 1,3 asymmetric induction argument in which the approach of the electrophile occurs *anti* to the C_5-phenyl ring substituent, with the planar *N*-Boc protecting group playing no part in the alkylation selectivity (Fig. 2). The *cis*-selectivity observed for alkylation of the enolate of auxiliary **4** is, however, less easily explained, and we reasoned that the opposing facial selectivity was a result of a chiral relay effect operating in the transition state to invert stereoselectivity. Two possible chiral relay transition states can be proposed; the first chiral relay transition state **1** would result in *cis*-enolate alkylation being controlled by the electrophile approaching *anti* to the *N*-benzyl protecting group which occupies a pseudo-axial position *anti* to the C_5 phenyl group (Fig. 3). An alternative transition state **2** would result in the *N*-benzyl group occupying a pseudo-equatorial conformation where steric interactions with the C_5 phenyl group would result in rotation around the *N*-benzylic bond locating the aromatic ring of the benzylic

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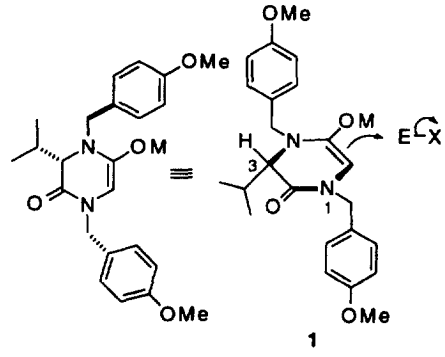

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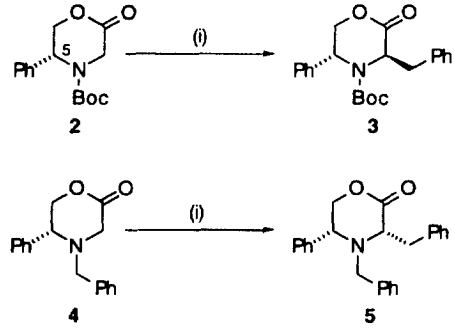
Electrophile attacks *anti* to both the C_3 isopropyl and N_1 protecting group.

Fig. 1.



Reagents and Conditions: (i) NaHMDS, BnBr, THF, -78 C

Scheme 1.

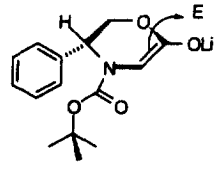
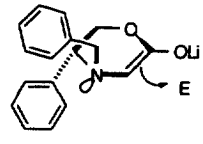


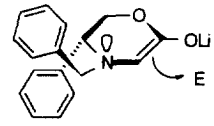
Fig. 2.



Transition State 1

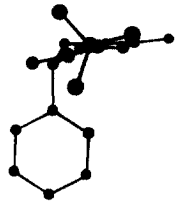
Fig. 3.

group being *anti* to the C_5 phenyl ring substituent. Once again, approach of the electrophile *anti* to the phenyl group of the *N*-benzyl group would result in *cis*-enolate alkylation (Fig. 4). Transition states 1 and 2 differ by the configuration of the readily epimerisable N-stereogenic centre. Molecular modelling studies[3] indicated that the structure of enolate **1** which invoked a pseudo-axial *N*-benzyl protecting group was more likely to be responsible for the observed *cis* selectivity since the conformation of enolate **1** was significantly lower in energy than the conformation of enolate **2** (Fig. 5).

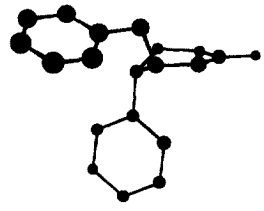


Transition State 2

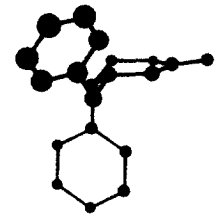
Fig. 4.



***N*-Boc-morpholinone Enolate**

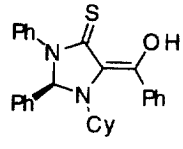


Enolate 1



Enolate 2

Fig. 5.



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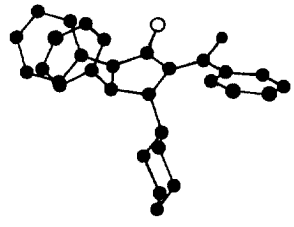


Fig. 6.

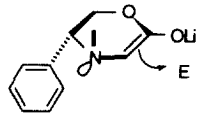


Fig. 7.

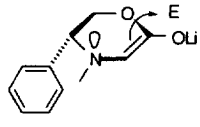
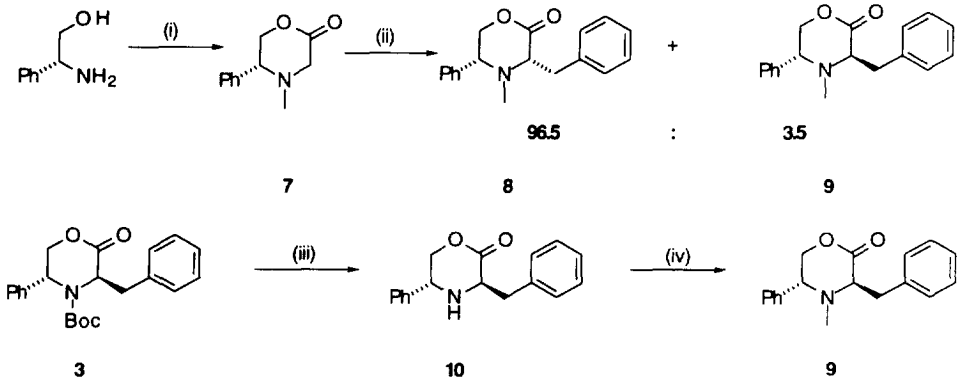


Fig. 8.

The results of these modelling studies were substantiated by inspection of the X-ray crystal structure of imidazolidine **6**, which has similar structural features to the enolate of **4**. It can be seen that the *N*-cyclohexyl group clearly occupies a pseudo-axial conformation (Fig. 6).[4]

In order to determine which of the two proposed chiral relay transition states was in operation, we prepared 4-methyl-5-phenyl morpholin-2-one **7** in which the *N*-benzyl group of auxiliary **4** had been replaced by an *N*-methyl protecting group. Alkylation studies on the enolate of auxiliary **7** would enable us to determine which of the proposed transition states was operating, since if the methyl group was occupying an axial position then the enolate conformation would result in *cis*-alkylated product **8** (Fig. 7); while a pseudo-equatorial methyl group would be unable to affect the facial selectivity of enolate alkylation resulting in a *trans*-alkylated product **9** *via* 1,3 asymmetric control from the 5-phenyl group (Fig. 8).[5]

5-Phenylmorpholin-2-ones **2**, **4**, and **7** were prepared from (*R*)-phenylglycinol in 54, 61, and 40% yield by a modification of the literature procedure, *via* a three-component coupling method.[2] Auxiliaries **2** and **4** were benzylated by deprotonation with LHMDS in THF at −78°C, and reaction with 5 equivalents of benzyl bromide to afford *trans*-benzylated **3** and *cis*-benzylated **5** in >99% and 93% d.e., respectively.[6] Having successfully reproduced the literature results for the known auxiliaries **2** and **4**,[2] *N*-methyl morpholin-2-one **7** was benzylated under identical conditions to afford a mixture of benzylated diastereoisomers in 93% d.e (Scheme 2). The diastereoisomers **8** and **9** were separated by chromatography, and the ^{1}H NMR spectroscopic data compared with those obtained for *trans*-**3** and *cis*-**5**, the results of which clearly suggested that the major diastereoisomer was the *cis*-benzylated auxiliary **8** ($[\alpha]_D^{23}$=+68.7, c=0.34, CH_2Cl_2). This stereochemical assignment was confirmed by comparison of the minor diastereoisomer with authentic *trans*-benzylated isomer **9**, which was obtained *via* deprotection of *trans*-**3** to afford secondary amine **10** and subsequently *N*-methylated to afford *trans*-benzylated **9** as a single diastereoisomer ($[\alpha]_D^{23}$=+27.8, c=0.32, CH_2Cl_2).



Reagents and Conditions: (i) Phenylbromoacetate, diisopropylethylamine, CH_3CN; MeI; (ii) LHMDS, BnBr, THF, -78°C; (iii) TFA, CH_2Cl_2; (iv) Na_2CO_3, MeI, DMF.

Scheme 2.

In conclusion, we have clearly demonstrated that the *cis*-selectivity observed for alkylation of the enolate of auxiliary **4** is consistent with a chiral relay system operating to invert the stereochemical information of the auxiliaries C_5 stereogenic centre. We are currently investigating other chemical scenarios where the application of chiral relay networks may be used to explain and enhance the stereoselectivity of enolate alkylation.

Acknowledgements

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References

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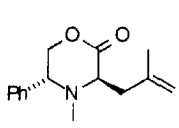
2. J. F. Dellaria Jr., B. D. Santarsiero, *Tetrahedron Lett.*, 1988, **47**, 6079; J. F. Dellaria Jr., B. D. Santarsiero, *J. Org. Chem.*, 1989, **54**, 3916.
3. Molecular modelling calculations were carried out using CS Chem3D Pro™ (CambridgeSoft Corp., 875 Massachusetts Ave., Cambridge, Massachusetts 02139 USA).



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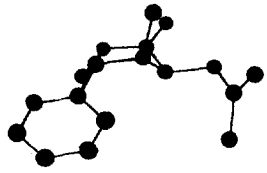

Fig. 9.

4. H. Benhaoua, F. Texier, L. Toupet, R. Carrié, *Tetrahedron*, **1988**, *44*, 1117.
5. Indirect evidence on the conformation of an *N*-methyl group morpholinone was gained from examining the X-ray crystal structure of **11** (Fig. 9) which clearly revealed a methyl group occupying a pseudo-axial position; C. Agami, D. Bihan, C. Puchot-Kadouri, *Tetrahedron*, **1996**, *52*, 9079.
6. We found that substitution of LHMDS for NaHMDS gave better yields of the monobenzylated auxiliaries.