

## Chiral relay auxiliaries\*

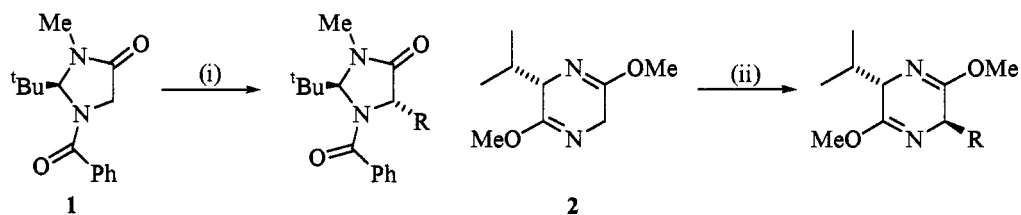
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**Abstract:** an alternative strategy for chiral auxiliary design is described where configurationally flexible moieties are employed to relay, inert, and amplify the stereochemical information of existing stereogenic centres via chiral relay networks, thus ensuring efficient control of asymmetric induction.

### INTRODUCTION

Chiral auxiliaries and templates are effective tools for the asymmetric synthesis of homochiral molecules.<sup>1</sup> Most chiral auxiliaries are small heterocyclic compounds which rely on sterically demanding functional groups to control the conformation of their ring systems. Under ideal circumstances, the conformation of an auxiliary should be constrained to ensure that its prochiral centre reacts with a reagent *via* diastereoisomeric transition states which are sufficiently different in energy to ensure that only a single diastereoisomer is formed as product. In order to maximise the diastereoselectivity observed for an auxiliary, it would appear reasonable that the stereocontrolling functional group adopts a position in space as close as possible to the newly forming stereogenic centre. Structural considerations dictate that realisation of this ideal is not always attainable and numerous examples of chiral auxiliaries that rely on relatively remote stereogenic centres to control diastereoselectivity are known. Alkylation of the enolates of Seebach's imidazolidinone (1),<sup>2</sup> or Schöllkopf's bis-lactim ether auxiliary (2),<sup>3</sup> for example, are controlled *via* 1,3- and 1,4- asymmetric induction respectively (scheme 1).



Reagents: (i) LDA, RX; (ii) <sup>n</sup>BuLi, RX

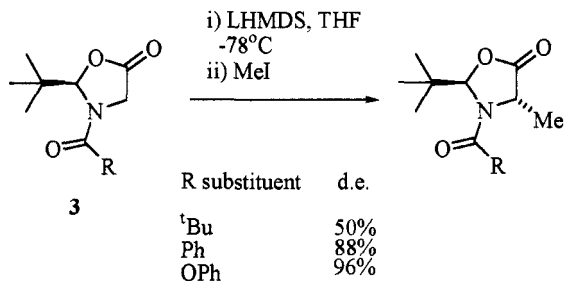
Scheme 1

### PRINCIPLES OF CHIRAL RELAY AUXILIARIES

A vast body of work has demonstrated that the factors which control the diastereoselectivities of chemical reactions are a complex function of both steric and electronic interactions, which combine to transfer, or

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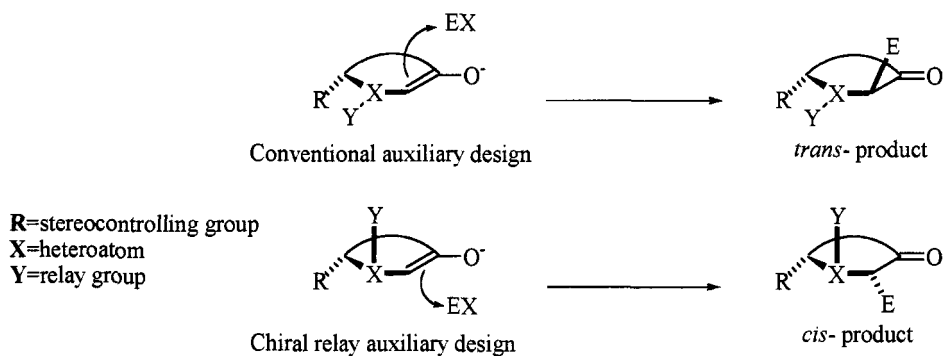
'relay', stereochemical information from the stereogenic centre to the site of reaction. The complex interplay of these interactions is often very subtle, and numerous examples exist where small changes in bond angles, or heteroatom hybridisation can result in large changes in diastereoselectivities. Seebach *et al.*, for example, have reported that modifying the *N*-protecting group of the imidazolidinone derived auxiliaries (**3**) results in large improvements in the observed diastereoselectivities during enolate alkylation (scheme 2).<sup>2</sup>



Changing protecting group improves diastereoselectivity

Scheme 2

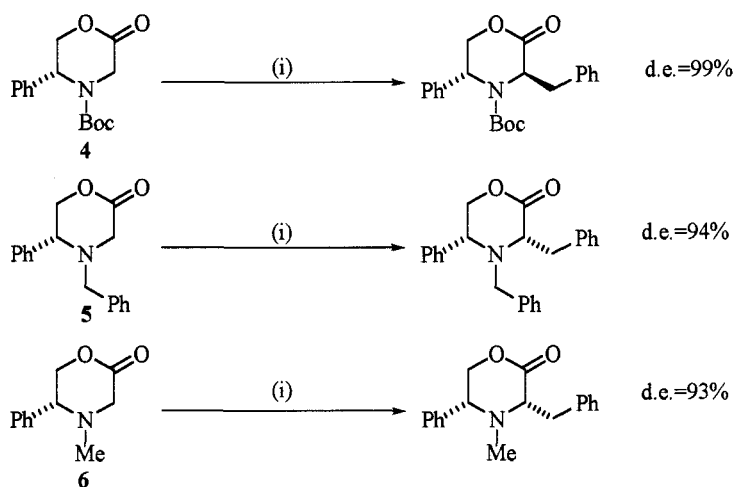
Since it is increasingly apparent that protecting groups do not always act as passive spectators, an alternative strategy for auxiliary design can be proposed in which an achiral conformationally flexible group is inserted between the stereogenic centre and the prochiral reactive centre (scheme 3). Steric interactions between the functional group **R** of the stereogenic centre and the conformationally mobile group **Y** serve to fix the relative 1,2- stereochemistry antiperiplanar, thus directing any incoming reactant at the prochiral centre *anti* to the conformationally mobile group. In ideal circumstances, the conformationally flexible group should serve to both relay, and amplify the stereochemical information of the existing stereogenic centre, thus enabling efficient control of diastereoselectivity.



Scheme 3

## CHIRAL AUXILIARIES EMPLOYING A SINGLE RELAY UNIT

It is important to note that the presence of a single chiral relay within a chiral auxiliary results in inversion of the stereodirecting information of the stereogenic centre, thus providing a simple diagnostic tool to determine when this type of effect is operating. Careful examination of the structures of known chiral auxiliaries revealed a morpholin-2-one based system where changing *N*-protecting group results in dramatic changes in facial selectivity. The enolate of *N*-Boc morpholinone **4** was benzylated in 99% d.e. with *trans*-selectivity, while the enolate of the corresponding *N*-benzyl morpholinone **5** was benzylated to afford the *cis*-product as the major diastereoisomer in 94% d.e. (scheme 4).<sup>4</sup>



Reagents and conditions: (i) LiHMDS, PhCH<sub>2</sub>Br, THF, -78°C

Scheme 4

While the selectivity observed for the *N*-Boc morpholin-2-one **4** was easily explained by invoking a conventional 1,3-asymmetric induction argument where the *N*-Boc protecting group plays no role in controlling facial selectivity, the reversal in selectivity observed for *N*-benzyl **5** was explained by invoking a chiral relay network. Studies on the corresponding *N*-methyl morpholinone **6** (*cis*-benzyl, 93% d.e.), revealed that the high *cis*-diastereoselectivity observed for **5** was a consequence of the conformation adopted by the enolate of the auxiliary, which was controlled by two cooperative effects:<sup>5</sup>

- (i) A stereoelectronic effect that places the nitrogen lone-pair in a *pseudo*-equatorial environment to avoid interaction with the  $\pi$ -system of the enolate.
- (ii) A chiral relay effect where the *N*-benzyl group occupies a *pseudo*-axial position *anti* to the C<sub>5</sub> phenyl group thus directing the incoming electrophile to the *Si* face of the enolate to afford *cis*-substituted product (figure 1).
- (iii)

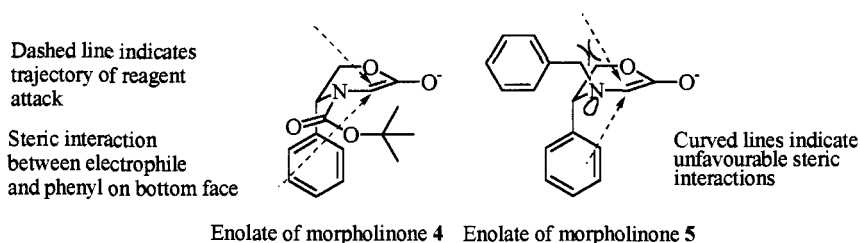
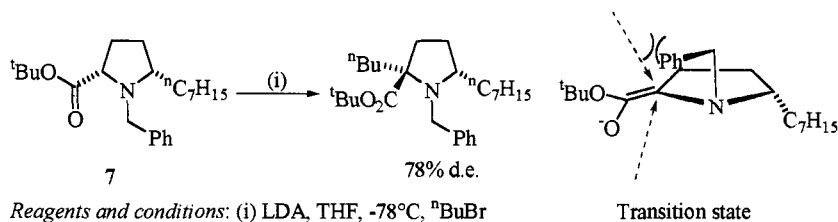


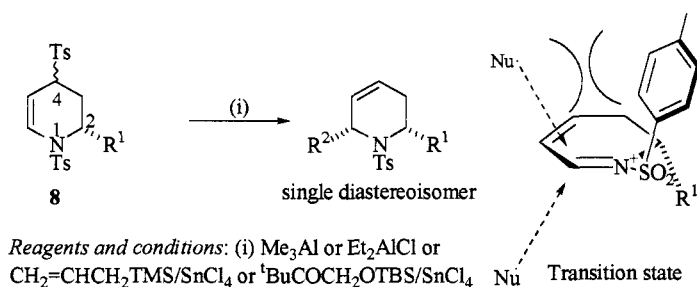
Figure 1

The apparently anomalous stereoselectivities reported for other chiral auxiliaries reported in the literature may also be rationalised by invoking a single chiral relay concept. Rapoport has reported a five-membered ring system **7**, where an exocyclic enolate is *cis*-alkylated in 78% d.e. It is likely that this selectivity is due to a chiral relay effect, similar to that operating in the morpholinone **5**, where the *N*-benzyl group is oriented *anti* to the heptyl side-chain (scheme 5).<sup>6</sup>



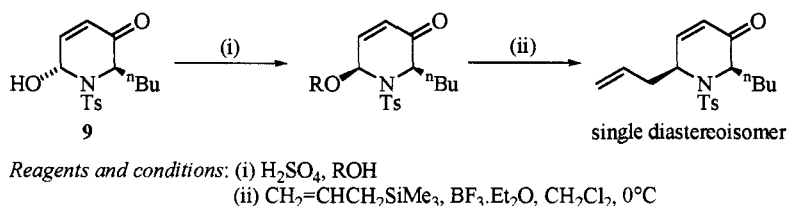
Scheme 5

Craig *et al.* have recently reported on a chiral auxiliary **8** based on the stereoselective alkylation of a cyclic iminium species. The iminium species is generated *via* an S<sub>N</sub>1 mechanism, since it was shown that the reaction proceeds with identical stereoselectivity regardless of the stereochemistry of the C<sub>4</sub> tosyl group. This iminium species is attacked by a nucleophilic species with high diastereoselectivity, to give the *syn* isomer as the exclusive product. A simple 1,3- asymmetric induction argument would predict that the reaction should proceed with *anti* selectivity, but instead, the tosyl group must clearly block the *Si*-face of the iminium species, thus inverting the stereochemical information of the C<sub>2</sub> substituent to afford *cis*-alkylated product (scheme 6).<sup>7</sup>



Scheme 6

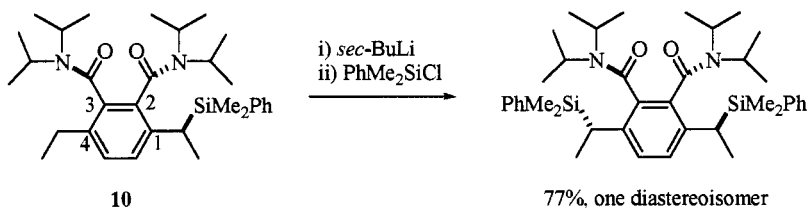
A similar mechanism is likely to be operating for the system described by Hopman *et al.* where an iminium ion is generated *in situ* from the unsaturated ketone **9**, and *cis*-alkylated by an allylic silane, (scheme 7).<sup>8</sup>



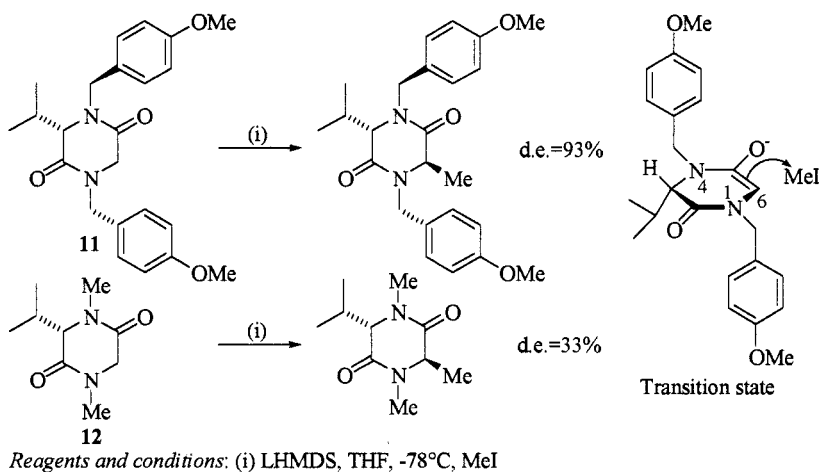
Scheme 7

## CHIRAL AUXILIARIES EMPLOYING TWO RELAY UNITS

The chiral relay approach is not confined to simple systems employing single relays. Clayden *et al.* have reported on a novel bis-amide aryl based system **10** which uses two tertiary amide units to transfer chiral information in a double relay system. The stereochemical information of the C<sub>1</sub> benzylic position fixes the conformation of the proximal amide unit at C<sub>2</sub> orthogonal to the aryl ring. This conformation ensures that the bulky diisopropyl unit is fixed *anti* to the phenyldimethylsilyl group, which in turn directs the diisopropyl unit of the C<sub>3</sub> amide unit *syn* to the phenyldimethylsilyl group at C<sub>1</sub>. This chiral relay network may be deployed for asymmetric synthesis by deprotonation of the C<sub>4</sub> benzylic position to afford a carbanion which is silylated *anti* to the bulky diisopropyl unit of the C<sub>3</sub> amide group (scheme 8).



This example serves to illustrate the general principle that while a single chiral relay unit results in net inversion of the original stereochemical information, two chiral relay units result in net retention of stereochemical information. In a similar vein, we have shown that a diketopiperazine (DKP) derived auxiliary **11** can employ a chiral relay network to control the diastereoselectivity of alkylation at its C<sub>6</sub> enolate. X-Ray crystallographic analysis of DKP **11** revealed that the isopropyl group at C<sub>3</sub> fixed the proximal N<sub>4</sub> *para*-methoxybenzyl group *anti*, which fixed the conformation of the distal N<sub>1</sub> *para*-methoxybenzyl group *syn* to the isopropyl group. The close proximity of the N<sub>1</sub> benzyl group to the point of enolate alkylation at C<sub>6</sub> results in very high d.e.s for this system (> 90% d.e. for all electrophiles). Evidence that a chiral relay network was in fact responsible for the very high d.e.s observed for this class of enolate was obtained from studies involving the *N,N*-dimethyl DKP enolate **12**, which was alkylated with a poor 33% d.e. (scheme 9).<sup>10</sup>



## CONCLUSION

The principle of using chiral relay networks to enhance asymmetric induction has been shown to be an effective mechanism for the preparation of homochiral molecules. This approach demonstrates that it is not always necessary for the stereodirecting group to be in close proximity to the newly forming stereogenic centre provided that the orientation of any intervening conformationally mobile groups can be efficiently controlled. Incorporation of these powerful ideas into the design of chiral auxiliaries ensures that efficient amplification and inversion of stereochemical information can occur. It is highly likely therefore that the further application of this powerful tool to other scenarios will lead to a new generation of highly efficient chiral auxiliaries.

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