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Addition to Activated Imines of Enolates from Chiral *N*-Acyloxazolidinones

Isaac Abrahams, Majid Motevalli, Andrew J. Robinson and Peter B. Wyatt*

Department of Chemistry, Queen Mary and Westfield College, University of London, Mile End Road, London E1 4NS, UK

Abstract: The lithium and titanium enolates of *N*-acyloxazolidinones **1a-c** add in their chelated forms to PhCH=NTs, to give stereoselectively the β-amino acid derivatives **3a-c** and **4a-c**. The relative configurations of the newly created chiral centres were established by conversion to the *trans* (**8a-c**) or *cis* (**9a, c**) β-lactams. Absolute stereochemistry was assigned by correlation with known compounds **10a** and *ent*-**11a**, together with an X-ray crystal structure determination on **9a**. The use of the lithium enolate of **1a** at -78 °C gave only a 1.4:1 ratio of *anti* product **3a** to *syn* product **4a**, but this ratio was improved to >5:1 by the use of the chlorotitanium enolate of **1a** at -55 °C or below. Similar results were obtained by using the chlorotitanium enolate of **1b**, but for the chlorotitanium enolate of the *N*-(phenylacetyl)oxazolidinone **1c** the proportion of *syn* product **4c** to *anti* product was significantly greater, consistent with a kinetically controlled reaction involving the *si* face of the chelated (*Z*)-enolate and the competing alternative transition states **TS3** (reaction on *si* face of imine) and **TS7** (reaction on *re* face of imine).

Introduction

The enantioselective synthesis of β-amino acids and β-lactams is important because these units occur in many antibiotics and alkaloids.[1] The main synthetic strategies that have been adopted are: (i) addition of enolate equivalents to imines,[2] (ii) [2+2] cycloadditions of ketenes with imines (Staudinger reaction)[3] and (iii) conjugate additions of amines[4] or their metal salts[5-8] to α,β-unsaturated carbonyl compounds. There have been several reports of the use in strategy (i) of enolates bearing a chiral auxiliary.[9,10] Evans, in discussing the reactions of chiral enolates with 2-phenylsulfonyl-3-phenyloxaziridine, has written in a footnote that sodium and lithium enolates from *N*-acyloxazolidinones reacted quantitatively with *N*-(benzylidene)benzenesulfonamide to give aldol-type adducts.[11] We are unaware of any discussion of the stereochemical outcome of this particular reaction, even though the corresponding additions of such enolates to aldehydes have attracted considerable interest.[12-16] Recently Boger and Honda[17] described studies involving the addition of tin (II), boron and titanium (IV) enolates of *N*-acyloxazolidinones to pyridine-2-carboxaldimines. They found that only the tin enolates gave good yields and that the product distribution was consistent with a preference for reaction *via* a transition state wherein the pyridine nitrogen, but not the oxazolidinone carbonyl group, co-ordinated to the metal atom: *i.e.* the 'nonchelated' transition state was the favoured one.

Here we describe our studies of the reactions between lithium and titanium enolates of *N*-acyloxazolidinones and activated benzaldimines: the enolates were found to react in chelated form and to show selectivity between the *syn* and *anti* products.

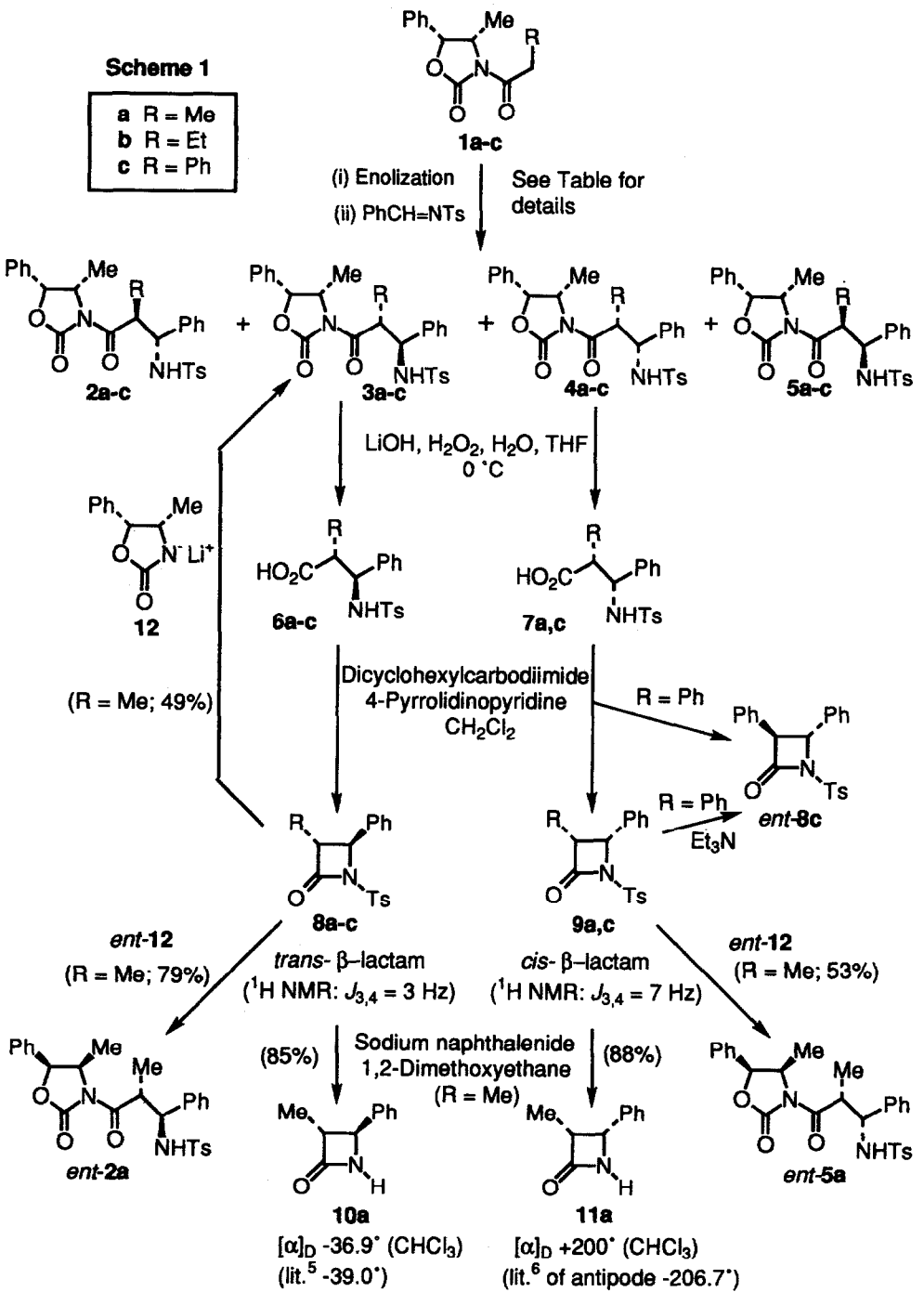

Scheme 1
a R = Me
b R = Et
c R = Ph
1a-c
(i) Enolization
(ii) PhCH=NTs
See Table for details
2a-c
3a-c
4a-c
5a-c
LiOH, H2O2, H2O, THF
0 °C
12
6a-c
7a,c
Dicyclohexylcarbodiimide
4-Pyrrolidinopyridine
CH2Cl2
(R = Me; 49%)
R = Ph
ent-8c
Et3N
8a-c
9a,c
ent-12
(R = Me; 79%)
trans- β-lactam
(1H NMR: J3,4 = 3 Hz)
cis- β-lactam
(1H NMR: J3,4 = 7 Hz)
ent-12
(R = Me; 53%)
(85%)
Sodium naphthalenide
1,2-Dimethoxyethane
(R = Me)
(88%)
ent-2a
ent-5a
10a
11a
[α]D -36.9° (CHCl3)
(lit.5 -39.0°)
[α]D +200° (CHCl3)
(lit.6 of antipode -206.7°)

Table 1. Addition of Enolates to PhCH=NTs under Various Conditions. Optimum procedures are shown in bold type.

Entry	R	Enolization Reagent (Equivalents) and Solvent	Conditions[a]	% yields[b] 3	4
1	Me	LDA (1.1)/THF	-78 °C/6 h	40	28
2	Me	LDA (1.1)/THF	-55 °C/6 h	37.5	27.5
3	Me	LDA (1.1)/THF	-78 °C/2 h then -> 0 °C	25	24
4	Me	$TiCl_4$ (2.6)/EtN^iPr_2 (1.2)/CH_2Cl_2	-78 °C/5 h	47	8
5	**Me**	**$TiCl_4$ (2.6)/EtN^iPr_2 (1.2)/CH_2Cl_2**	**-55 °C/5 h**	**66**	**12.5**
6	Me	$TiCl_4$ (2.6)/EtN^iPr_2 (1.2)/CH_2Cl_2	-78 °C/9 h/®	58	5
7	Me	$TiCl_4$ (2.6)/EtN^iPr_2 (1.2)/CH_2Cl_2	-78 °C /30 min, then 0 °C/30 min, then 20 °C/30 min	32	22
8	Me	$TiCl_4$ (2.6)/EtN^iPr_2 (1.2)/ THF	-55 °C/6 h/®	0	0
9	Me	$TiCl_4$ (1.0)/EtN^iPr_2 (1.2)/ CH_2Cl_2 (*see note c*)	-55 °C/6 h/®	7.5	<1
10	Me	LDA (1.1)/Et_2O-THF then $ClTi(O^iPr)_3$ (3.5)	-55°C/6h	0	<1
11	Me	LDA (1.1)/Et_2O-THF then $ClTi(O^iPr)_3$ (3.5)	-40 °C/2 h, then -> 20 °C	23	28
12	Me	$SnCl_4$ (2.6)/EtN^iPr_2 (1.2)/CH_2Cl_2	-78 °C/5 h	0	0
13	Et	$TiCl_4$ (2.6)/EtN^iPr_2 (1.2)/CH_2Cl_2	-78 °C/6 h/®	50	7
14	**Et**	**$TiCl_4$ (2.6)/EtN^iPr_2 (1.2)/CH_2Cl_2**	**-55 °C/5 h/®**	**74**	**8**
15	**Ph**	**$TiCl_4$ (2.6)/EtN^iPr_2 (1.2)/CH_2Cl_2**	**-78°C/7 h/®**	**22.5**	**74**
16	Ph	$TiCl_4$ (2.6)/EtN^iPr_2 (1.2)/CH_2Cl_2	-55 °C/7 h/®	24	68

a. The imine PhCH=NTs was normally added to the enolate solution except where the symbol ® is shown, denoting the reverse mode of addition.

b. Reported yields of **3** and **4** are normally after isolation by flash chromatography, except for product **4** in entries 8, 9, 12, 13 and 14 where the yields were estimated by NMR spectroscopy. In none of the above cases were isomers **2** and **5** observed, although when the reaction of the lithium enolate with R = Ph was performed for 6 h at -70 °C, NMR spectroscopy showed that the principal products, which could not be separated chromatographically, were **4c** and an unidentified oxazolidinone in the ratio 6:5.

c. Here the imine was *not* complexed with $TiCl_4$ before being mixed with the chlorotitanium enolate.

RESULTS AND DISCUSSION

(i) Determination of Product Stereochemistry and of Optimum Conditions for the Reaction of the N-*Propionyloxazolidinone 1a with* N-*(Benzylidene)toluene-4-sulfonamide (PhCH=NTs)*

First we investigated the stereochemical course of the reaction between the lithium enolate of the *N*-propionyloxazolidinone **1a** and the imine *N*-(benzylidene)toluene-4-sulfonamide (Scheme 1 and Table 1, entries 1-3). When enolization was effected using lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -78 °C, two main diastereomeric products **3a** and **4a** could be isolated by flash chromatography. The relative configurations of the two newly created chiral centres in each of these products were established by removal of the oxazolidinone chiral auxiliary according to the general method of Evans[18] (LiOH, H_2O_2, THF-H_2O), followed by cyclization to the corresponding β-lactams **8a** and **9a** using Tanner's conditions (dicyclohexylcarbodiimide and 4-pyrrolidinopyridine).[19] The β-lactams could be distinguished by their ^1H NMR spectra, using the azetidinone coupling constants $J_{3,4}$: compound **8a** had J = 3 Hz, and so was the *trans* β-lactam, corresponding to *anti* relative stereochemistry in the compound **3a**, whereas the β-lactam **9a** had J = 7 Hz, consistent with *cis* relative stereochemistry and with its precursor **4a** being the *syn* isomer.

Detosylation of the two β-lactams could be performed without any epimerization, using sodium naphthalenide in DME. The absolute configurations of the resultant *trans* and *cis* *N*-protio β-lactams **10a** and **11a** were then assigned by comparison of their specific rotations with the values reported by Davies,[5,6] who has recently described the preparations of **10a** and of *ent*-**11a** (by asymmetric conjugate addition reactions) and has correlated these substances with β-phenyl-β-alanine, the absolute configuration of which was already known.

We obtained additional evidence for the absolute configuration of compound **4a** from a single-crystal X-ray diffraction study[20] of the β-lactam **9a**: using the software package ***SHELXL93*** [21] it was found that the structure shown in Fig 1 fitted the crystallographic data better than did the enantiomer *ent*-**9a**.

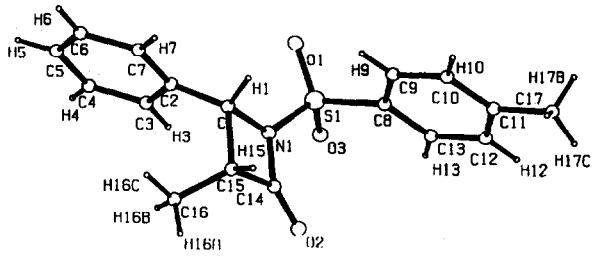


Fig 1. X-ray crystal structure of the β-lactam **9a**.

The enolate-imine reaction illustrated in Scheme 1 could, in principle, also yield the diastereomers **2a** and **5a**. Since we had not been able to isolate these compounds from the reaction mixture, we decided to prepare authentic samples of the enantiomers of both these substances, for use as spectroscopic and

chromatographic standards. We considered that the presence of the *N*-sulfonyl group in the β-lactams **8a** and **9a** would facilitate their opening by nucleophiles.[22] When the β-lactam **8a** was treated with the lithium salt of (4*R*,5*S*)-4-methyl-5-phenyloxazolidin-2-one (**12**), ring cleavage did indeed occur and the acyloxazolidinone **3a** which resulted (49 % yield) was identical to the sample prepared originally. The lithium salt of (4*S*,5*R*)-4-methyl-5-phenyloxazolidin-2-one (*ent*-**12**) was then used similarly to convert the β-lactams **8a** and **9a** into the acyloxazolidinones *ent*-**2a** and *ent*-**5a** respectively (79 and 53 % yields). Comparison of the 250 MHz ^{1}H NMR spectra of *ent*-**2a** and *ent*-**5a** with that of the crude product from the lithium-mediated reaction at -78 °C (Table 1, entry 1) suggested that negligible amounts (< 1 %) of isomers **2a** and **5a** had been produced in this reaction and that the ratio of **3a** to **4a** was 1.4:1. When the reaction was repeated at -55 °C (entry 2) **3a** and **4a** were again the predominant products, but there were slight losses in both yield and selectivity. Allowing the reaction mixture to warm up to 0 °C before it was quenched (entry 3) gave **3a** and **4a** in a 1:1 ratio, with a further reduction in the yield.

Titanium enolates have been found to show good stereoselectivity in their reactions with aldehydes[16] and with imines.[23] We therefore examined the enolization of **1a** using $TiCl_4$ and $^iPr_2NEt$ in dichloromethane, followed by reaction with the complex of *N*-(benzylidene)toluene-4-sulfonamide and $TiCl_4$. The same two products **3a** and **4a** predominated as in the lithium-mediated reaction, but the total yields tended to be somewhat higher and the selectivity was also better. For the reaction at -55 °C (entry 5) the ratio of **3a** to **4a** in the crude product, as determined by 250 MHz ^{1}H NMR spectroscopy, was 5.3:1; again isomers **2a** and **5a** could not be detected. If the reaction mixture was allowed to warm up from -78 °C to +20 °C before quenching (entry 7), then the selectivity was greatly diminished, which is consistent with the onset of thermodynamic control. No reaction occurred when THF was used as the solvent in place of dichloromethane (entry 8), presumably because the Lewis acidity of the titanium was reduced by the co-ordinated THF. Entry 9 shows that reduction of the amount of $TiCl_4$ from 2.6 to 1.0 equivalents led to a much lower yield, with much unchanged starting material; again compound **3a** was favoured over compound **4a**.

Thornton[15] has described an alternative procedure for titanium enolate formation, by exchange of the lithium enolate with excess $ClTi(O^iPr)_3$ in ethereal solvents. When we attempted to do this in ether-THF at -55 °C (entry 10) the only detectable addition product was **4a**, but the yield was <1 % and much starting material remained unchanged. The titanium enolate thus generated was therefore much less nucleophilic in an ethereal solvent than the original lithium enolate; intriguingly this titanium enolate appeared to favour the formation of the *syn* product. By allowing the reaction mixture to attain room temperature before work up (entry 11) both **3a** and **4a** could be isolated (23 % and 28 % respectively).

An attempt to form a tin (IV) enolate by using $SnCl_4$-$^iPr_2NEt$ in place of $TiCl_4$-$^iPr_2NEt$ (entry 12) did not lead to any addition products.

Thus, of all the procedures investigated, the conditions of entry 5 (excess $TiCl_4$ with EtN^iPr_2 in dichloromethane) were found to be the best for stereoselective formation of the *anti* product **3a**. The applicability of these conditions to other substrates was then examined.

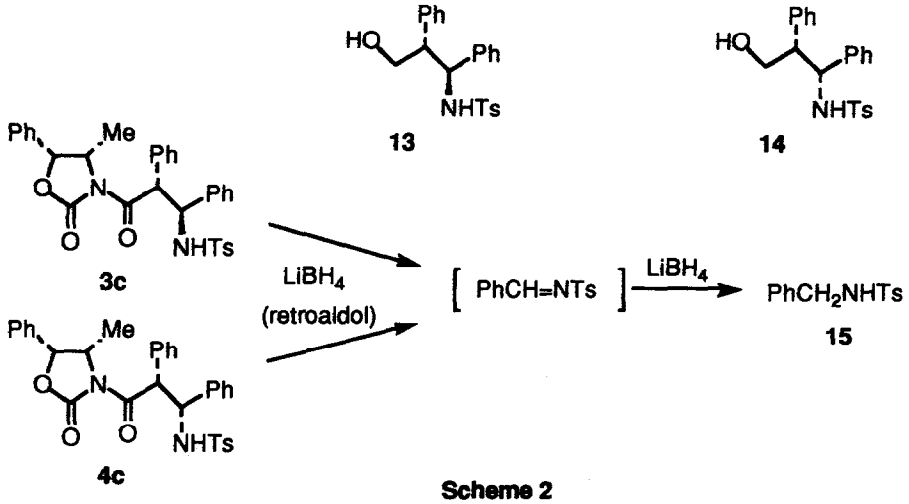
(ii) Experiments Using the* N-*Butyryl- and* N-*Phenylacetyl- Oxazolidinones 1b and 1c

The titanium-mediated reactions of the *N*-butyryloxazolidinone **1b** with PhCH=NTs (Table 1, entries 13 and 14) proceeded in similar yields and with comparable levels of diastereoselectivity to those of the

corresponding *N*-propionyloxazolidinone **1a**. The *anti* relative stereochemistry in the major product **3b** was established by cyclization to the *trans* β-lactam **8b**.

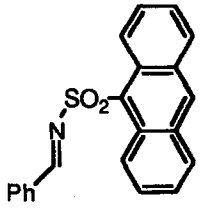
The *N*-phenylacetyloxazolidinone **1c** added to PhCH=NTs in the presence of $TiCl_4$ and EtN^iPr_2 (entries 15 and 16) to give the products **3c** and **4c** in combined chemical yields exceeding 92 %: it is likely that the presence of the conjugating phenyl group facilitates the enolization process. The minor addition product is considered to be the *anti* adduct **3c**, since removal of the chiral auxiliary and cyclization gave a *trans* β-lactam, presumed to be **8c**, although assignment of its *absolute* configuration is somewhat tentative. Surprisingly, similar treatment of the major addition product **4c** also gave predominantly a *trans* β-lactam, which was enantiomeric with that obtained from the minor addition product. However, a small amount of the *cis* β-lactam **9c** was also formed and was shown by NMR spectroscopy to epimerize smoothly to give *ent*-**8c** upon treatment with triethylamine (1 equivalent) in $CDCl_3$. We infer that the major addition product has the *syn* configuration **4c** but that attempted formation of the *cis* β-lactam **9c** leads to extensive epimerization in favour of the thermodynamically more stable *trans* β-lactam *ent*-**8c**. Such a process would be expected to occur most easily at that chiral centre which is both benzylic and α to the carbonyl group. Thus, before the epimerization, the two adducts **3c** and **4c** formed in the enolate-imine reaction must both have had the same configuration at the centre α to the carbonyl group and so must both have arisen by attack upon the same face of the enolate. We presume that this is the *si* face, since the titanium enolate from **1a** reacted with the same imine exclusively at the *si* face.

We attempted to prove the absolute configurations of the new chiral centres by reductive removal of the oxazolidinone units using $LiBH_4$,[24] in the expectation of forming the alcohols **13** and **14**, which are *N*-tosyl derivatives of known amino alcohols.[25] However, in both cases we isolated only *N*-tosylbenzylamine (**15**, Scheme 2), consistent with cleavage of **3c** and **4c** by retro-aldol reactions, followed by reduction of the resultant imine PhCH=NTs.

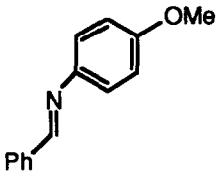


Scheme 2

The *anti/syn* ratios observed in the $TiCl_4$-mediated reactions of the *N*-phenylacetyloxazolidinone **1c** are much lower than in the corresponding reactions of the *N*-propionyl and *N*-butyryl oxazolidinones, **1a** and **1b**. It was considered possible that the susceptibility of the products **3c** and **4c** to retro-aldol reactions and perhaps to epimerization might result in thermodynamic control, even at low temperatures. However, when pure specimens of the two diastereomers **3c** and **4c** were treated separately with $TiCl_4$ and EtN^iPr_2 in CH_2Cl_2 at -55 °C for 3.5 h, no isomerisation could be detected by NMR spectroscopy.



16



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(iii) Experiments Using Other Imines

A significant disadvantage associated with the use of the *N*-tosyl group for the protection and activation of imines is the need to use vigorous conditions, typically involving metallic sodium, to effect cleavage of the nitrogen-sulfur bond. We therefore examined the addition of enolates from the *N*-propionyloxazolidinone **1a** to benzaldimines bearing other substituents on nitrogen.

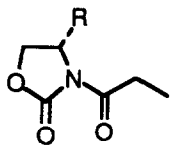
We have recently reported[26] that Reformatsky reactions of the anthracene-9-sulfonylimine **16** yield protected β-amino acids and that *N*-deprotection is readily achieved using aluminium amalgam. However, the reaction of the imine **16** with the lithium enolate of **1a** at -78 °C gave a 39 % combined yield of two diastereomeric adducts which could not be separated, whereas use of the $TiCl_4$-EtN^iPr_2 procedure for enolization did not lead to any addition. Hart *et al.*[9] have successfully used the lithium enolates from esters of a chiral alcohol in reactions with *N*-(4-anisyl)imines. The anisyl group could be removed by mild oxidation. Our attempt to add the lithium enolate of **1a** to *N*-(benzylidene)-4-anisidine in THF (-55 °C/6h) gave mainly unreacted starting materials. These results were disappointing, but are understandable in view of the bulkiness of the anthracene-9-sulfonyl group and the poorly electron-withdrawing nature of the *N*-anisyl group.

The *N*-tosylimines were thus found to be by far the most suitable partners for enolates of the Evans type, but it is recognised that it would be worthwhile to develop a *N*-protecting group for imine nitrogen that gives sufficient activation to allow the addition of modest nucleophiles, whilst being removable under mild conditions (*e.g.* by catalytic hydrogenation).

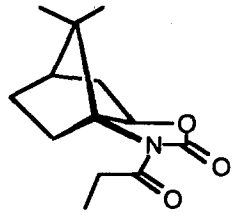
(iv) Rationalisation of the Observed Stereoselectivity

Where kinetic control operates, as appears to be the case for those enolate-imine reactions which we have performed at -55 °C or below, the product stereochemistry can be interpreted in terms of likely transition states. Possible structures of transition states in aldol reactions have been the subject of considerable interest lately[12,14,16] and examples of the related reaction between enolates and imines have also been discussed.[17,23,27] The same two diastereomers **3a** and **4a** are formed in the Li- and Ti-mediated reactions of the *N*-propionyloxazolidinone **1a** with *N*-(benzylidene)toluene-4-sulfonamide. Both these products correspond to reaction on the *si* faces of the enolates, which are less sterically hindered than the corresponding *re* faces if the enolates react in the chelated form and have the (*Z*)-geometry. Such facial selectivity is usual

in alkylation reactions[24] but contrasts with Boger's studies[17] where it was concluded that, in adding to pyridine-2-carboxaldimines, tin(II) and titanium(IV) enolates reacted preferentially in their non-chelated forms because the pyridine nitrogen co-ordinated to the metal atom. The aldol reactions of certain enolates derived from *N*-acyloxazolidinones have been described in the literature. Both the lithium and tri(isopropoxy)titanium enolates of the *N*-propionyloxazolidinone **18a** gave mainly the products derived from chelation control when they reacted with benzaldehyde:[14] ratios varied from 87:13 to 97:3 according to conditions. However, chlorotitanium enolates of **18b** and of **19** have both been reported to react mainly in their non-chelated forms when adding to aldehydes.[28,16]



18a R = ^{i}Pr
18b R = $PhCH_2$



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A possible factor favouring chelation control in the reactions of chlorotitanium enolates with imines is that, because nitrogen is less electronegative than oxygen, the dipole-dipole repulsion of the imine C=N bond with the imide carbonyl groups in a cyclic transition state, such as **TS 1** in Fig. 2, is smaller than would occur for the C=O group of the aldehyde in **TS 2**. Alternatively, the relatively low electrophilicity of imines and the steric effect of the *N*-tosyl group may require the reaction to procede through an open transition state, such as **TS 3**, in which two metal atoms are involved, one of which activates the imine, thus leaving the other more available for chelation with the imide oxygen atoms.

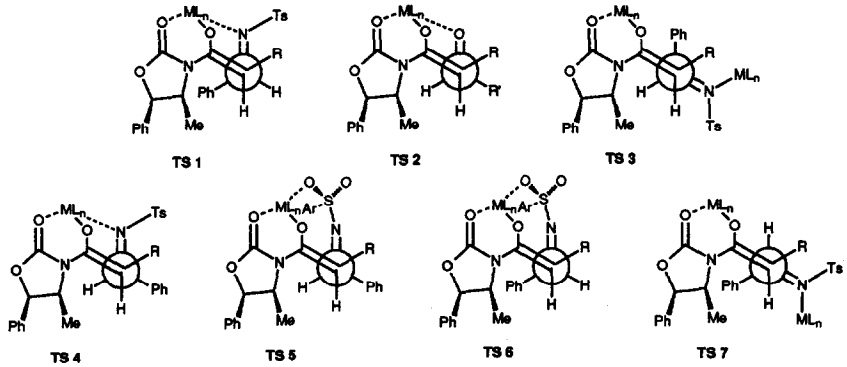

Fig. 2. Newman projections of possible transition states for enolate-imine and aldol reactions. ML_n represents a metal atom and its ligands. **TS1, TS 3** and **TS 6** correspond to product **3**, whereas **TS4, TS5** and **TS 7** correspond to product **4**. **TS 2** is an aldol transition state for comparison.

The *anti* product **3a** is favoured over the *syn* product **4a** in the reactions performed at low temperatures, induced by LDA and $TiCl_4$-EtN^iPr_2, indicating that there is a kinetic preference for reaction at the *si* face of the imine. One possible transition state for the formation of the *anti* product **3a** is **TS 1**, which is of the Zimmerman-Traxler type,[29] with the reaction occurring within a chair-type six membered ring. Here one metal atom is used to co-ordinate the oxazolidinone and enolate oxygen atoms as well as the imine nitrogen. An important difference between this transition state and the corresponding one (**TS 2**) for the aldol reaction of an aldehyde (which would be expected to react preferentially on the *re* face and to yield a *syn* product, as seen for the reaction between the lithium enolate of **18a** with benzaldehyde[14]) is the presence of a substituent on the imine nitrogen. Not only must the tosyl group adopt an axial position and thus experience a 1,3-repulsion with the R group, but if the imine has the (*E*)-configuration then the phenyl substituent will also be axial and thus approach closely to the oxazolidinone ring. An alternative transition state which would also give product **3a** is the open transition state **TS 3**, in which the enolate C=C and imine C=N are *anti* to one another. This has the advantage of removing the 1,3-diaxial interactions and the dipole-dipole repulsions between the C-O and C=N bonds in **TS 1**, at the cost of a gauche interaction between the R and Ph groups and the need for simultaneous participation of two metal atoms. Such a mechanism would account for the great reduction in yield when only one equivalent of $TiCl_4$ was used (entry 9). In the analogous titanium-mediated aldol reactions it was not necessary to use a large excess of the Lewis acid,[16] but for aldol reactions of boron enolates the amount of added $SnCl_4$ has been found to influence strongly the stereochemistry of the product and this has been interpreted in terms of an open transition state.[13]

Transition states **TS 4**, **5** and **7** involve reaction between the *si* face of the enolate with the *re* face of the imine and so could lead to the *syn* product **4a**; **TS 4** differs from **TS 1** in having the (*Z*)- geometry of the imine, thus avoiding the close approach of the phenyl group to the oxazolidinone ring. Annunziata *et al.*[23] have used ^1H NMR spectroscopy to study the complex of (*E*)-*N*-(benzylidene)aniline with $TiCl_4$ in CD_2Cl_2. They failed to detect any isomerization in the temperature range -70 °C to -10 °C and suggested that that *N*-arylimines were unlikely to react in the (*Z*)-geometry. Our imine (PhCH=NTs) exists as a single geometrical isomer, as judged by NMR spectroscopy in $CDCl_3$ at room temperature in the absence of Lewis acid; as the imine would not be expected to isomerize easily, we consider **TS 4** to be improbable. **TS 5** has the (*E*)-imine geometry, but involves co-ordination of the metal to the sulfonyl oxygen, rather than to the imine nitrogen. Such a transition state could explain the substantial amount of the *syn* product **4a** formed when the lithium enolate was used. However, formation of the major *anti* product **3a** is unlikely to occur through the related transition state **TS 6** since this would require the imine to adopt the (*Z*)-geometry. Davis *et al.*[30] have observed high levels of asymmetric induction in the addition of lithium enolates to *N*-arylsulfinylimines where the sulfinyl group was the only source of chirality and they have suggested a transition state in which lithium is co-ordinated to the sulfinyl oxygen. **TS 7** is an open transition state which would be expected to lie higher in energy than the related **TS 3** since the phenyl and oxazolidinone rings approach closely; however, steric interactions between the phenyl and R substituents are lower in **TS 7** than in **TS 3**, so that for large R the preference for **TS 3** over **TS 7** would be expected to diminish. Entries 15 and 16 in Table 1 show that, for chlorotitanium enolates, the presence of the bulky group R = Ph did indeed lead to a lower *anti*/*syn* ratio than was found for the sterically less demanding substituents R = Me and R = Et.

Conclusions

N-Sulfonylimines are effective electrophilic partners for the lithium enolates of *N*-acyloxazolidinones, as originally stated by Evans,[11] and also for the corresponding chlorotitanium enolates. In both systems reaction at the less hindered face of the chelated (*Z*)-enolates is strongly preferred. The use of EtN^iPr_2 and $TiCl_4$ for enolization is an economical and convenient method which gives selectivity between the *anti* product (thought to arise *via* open transition state **TS 3**) and the *syn* product (probably formed *via* **TS 7**).

Although the *N*-tosyl group can be removed from uncomplicated substrates without significant side reactions, there is a continuing need to develop a group which is sufficiently electron-withdrawing to activate the imine C=N towards the addition of weak nucleophiles, but which may easily be cleaved when no longer needed.

EXPERIMENTAL

Materials and General Procedures

The (4*S*,5*R*)-3-acyl-4-methyl-5-phenyloxazolidin-2-ones (**1a-c**)[31] and *N*-(benzylidene)toluene-4-sulfonamide[32] were prepared by literature methods. 'Petrol' refers to the light petroleum fraction bp 40-60 °C and was redistilled. 'Ether' is diethyl ether. '1.5 M LDA' refers to a 1.5 M solution in cyclohexane of lithium diisopropylamide mono(tetrahydrofuran) complex, purchased from the Aldrich Chemical Company. THF, 1,2-dimethoxyethane (DME) and (where appropriate) ether were dried by distillation from sodium and benzophenone. Dichloromethane was dried by distillation from calcium hydride. All mass spectra were recorded in electron impact mode. Unless stated otherwise, all experiments (including $[\alpha]_D$ measurements) were performed at 25 °C.

Organic Synthesis

Reaction Between N-*(Benzylidene)toluene-4-sulfonamide and the Lithium Enolate from (4*S*,5*R*)-4-Methyl-5-phenyl-3-propionyloxazolidin-2-one (**1a**).* To a solution of **1a** (233 mg, 1 mmol) in THF (5 mL) at -78 °C was added 1.5 M LDA (0.73 mL, 1.1 mmol) and the mixture was stirred for 0.5 h. To the resultant orange solution was added a solution of *N*-(benzylidene)toluene-4-sulfonamide (259 mg, 1 mmol) in THF (5 mL) and the mixture was stirred at -78 °C for 6 h, followed by quenching at -78 °C with saturated aqueous ammonium chloride (20 mL). The mixture warmed to 20 °C and was then extracted with ether (3 x 20 mL). Drying and evaporation of the ether layer gave a crude product which was considered on the basis of its 250 MHz ^1H NMR spectrum to contain, *inter alia*, compounds **3a** and **4a** in the ratio of 1.4 : 1. Compounds **2a** and **5a** were not detectable and so neither of these could have been formed in a yield exceeding 1 %. Purification by flash chromatography [CH_2Cl_2-petrol (1:1 to 1:0 gradient) then CH_2Cl_2-ether (49:1)] gave a mixture of **3a** and **4a** (347 mg, 70 %), which was fractionated by further flash chromatography [CH_2Cl_2-ether (99:1 to 19:1 gradient)].

The first product to elute was *(4*S*,5*R*)-4-methyl-3-[(2*R*,3*S*)-2-methyl-3-phenyl-3-(tosylamino)propionyl]-5-phenyloxazolidin-2-one* (**3a**) (196 mg, 40 %), which was recrystallised from EtOAc-petrol to give white needles, m.p. 153-154 °C; $[\alpha]_D$ -112 ° (*c* 1.07 in EtOAc); (Found: C, 65.6; H, 5.7; N, 5.6. $C_{27}H_{28}N_2O_5S$ requires C, 65.6; H, 5.7; N, 5.7 %); IR (KBr): ν = 3266, 1751, 1699 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 0.82 (d, 3 H, *J* = 6.6 Hz, ring -CH_3), 1.08 (d, 3 H, *J* = 6.7 Hz, chain -CH_3), 2.28 (s, 3 H, Ts-CH_3),

4.35 (dq, 1 H, *J* = 8.5 and 6.7 Hz, chain CH_3CHCH), 4.50 (dd, 1 H, *J* = 10.0 and 8.5 Hz, $CHCHNH$), 4.75 ('quintet', 1 H, *J* = 6.6 Hz, ring CH_3CHCH), 5.65 (d, 1 H, *J* = 7.1 Hz, ring $PhCHCH$), 5.99 (d, 1 H, *J* = 10.0 Hz, $CHNH$), 6.98-7.11 (m, 7 H, Ph and Ts-H_2) and 7.25-7.45 (m, 7 H, Ph and Ts-H_2); ^1H NMR assignments were supported by a ^1H-^1H decoupling experiment: when the methyl doublet at δ = 0.82 was irradiated, the 'quintet' at δ = 4.75 collapsed to a doublet (*J* = 6.6 Hz) and when the benzylic doublet at δ = 5.65 was irradiated, the 'quintet' at δ = 4.75 collapsed to a quartet (*J* = 7.1 Hz); MS: *m/z* (%) = 492 (M^+, 0.4), 337 (9.9), 260 (100), 177 (1.0), 160 (14.2), 156 (3.3), 131 (6.6); HRMS: found 492.1708 [calc for $C_{27}H_{28}N_2O_5S$ (M^+) 492.1719].

The second product, *(4S,5R)-4-methyl-3-[(2R,3R)-2-methyl-3-phenyl-3-(tosylamino)propionyl]-5-phenyloxazolidin-2-one* (**4a**) (140 mg, 28 %) was recrystallised from ether-petrol to give white cotton wool-like crystals (93 mg), mp 163.5-164.5 °C. $[\alpha]_D$ -46.6 ° (*c* 1.07 in EtOAc); (Found: C, 65.6; H, 5.7; N, 5.6. $C_{27}H_{28}N_2O_5S$ requires C, 65.6; H, 5.7; N, 5.7 %); IR (KBr): ν = 3301, 1771, 1686 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 0.40 (d, 3 H, *J* = 6.6 Hz, ring $-CH_3$), 1.27 (d, 3 H, *J* = 6.8 Hz, chain $-CH_3$), 2.29 (s, 3 H, Ts-CH_3), 4.36 ('quintet', 1 H, *J* = 6.9 Hz, chain CH_3CHCH), 4.66 ('quintet', 1 H, *J* = 6.7 Hz, ring CH_3CHCH), 4.79 (dd, 1 H, *J* = 9.1 and 8.0 Hz, $CHCHNH$), 5.29 (d, 1 H, *J* = 9.1 Hz, $CHNH$), 5.59 (d, 1 H, *J* = 7.5 Hz, ring $PhCHCH$), 7.00-7.07 (m, 7 H, Ph and Ts-H_2) and 7.16-7.53 (m, 7 H, Ph and Ts-H_2); ^1H NMR assignments were supported by a ^1H-^1H decoupling experiment: when the methyl doublet at δ = 0.40 was irradiated, the 'quintet' at δ = 4.66 collapsed to a doublet (*J* = 6.6 Hz) and when the benzylic doublet at δ = 5.59 was irradiated, the 'quintet' at δ = 4.66 collapsed to a quartet (*J* = 7.5 Hz); MS: *m/z* (%) = 337 (16.8), 260 (100), 233 (8.6), 177 (2.4), 160 (31.3), 155 (50.9), 131 (0.9); HRMS: found 337.1561 [calc for $C_{20}H_{21}N_2O_3$ (M - $C_7H_7O_2S$) 337.1552].

A similar reaction to the preceding one was performed at -55 °C rather than -78 °C. Isolated products were **3a** (184 mg, 37.5 %) and **4a** (135 mg, 27.5 %).

Reaction Between N-*(Benzylidene)toluene-4-sulfonamide and the Enolate from (4S,5R)-4-Methyl-5-phenyl-3-propionyloxazolidin-2-one (1a), Titanium (IV) Chloride and Diisopropylethylamine.* To a solution of **1a** (233 mg, 1 mmol) in CH_2Cl_2 (4 mL) at 0 °C were added diisopropylethylamine (209 μL, 1.2 mmol) and titanium (IV) chloride (121 μL, 1.1 mmol); the resultant purple mixture (the 'Ti enolate') was stirred at 0 °C for 20 minutes. The 'Ti enolate' was then cooled to -78 °C and treated with titanium (IV) chloride (165 μL, 1.5 mmol) and *N*-(benzylidene)toluene-4-sulfonamide (389 mg, 1.5 mmol) in CH_2Cl_2 (4 mL) (premixed at -5 °C). The mixture was stirred at -78 °C for 5 h and then quenched with saturated aqueous ammonium chloride (20 mL). The mixture was allowed to warm to 20 °C and was then extracted with CH_2Cl_2 (3 x 20 mL). Flash chromatography as before gave **3a** (232 mg, 47 %) and **4a** (39 mg, 8 %).

A Ti-mediated reaction was performed similarly to the preceding experiment, but at -55 °C rather than -78 °C. The crude product was examined by 250 MHz ^1H NMR spectroscopy. Compounds **3a** and **4a** were present in the ratio of 5.25 : 1. Compounds **2a** and **5a** were not detectable (*i.e.* the yield of each did not exceed 1 %). Isolated products were **3a** (324 mg, 66 %) and **4a** (62 mg, 12.5 %).

A similar Ti-mediated reaction was performed at -78 °C but the 'Ti enolate' was added to the imine-$TiCl_4$ mixture rather than *vice versa*. Isolated products were **3a** (287 mg, 58 %) and **4a** (25 mg, 5 %).

A similar reaction was attempted at -78 °C using $SnCl_4$ instead of $TiCl_4$. After aqueous work up the crude reaction mixture was examined by 80 MHz ^1H NMR spectroscopy. Products **2a**, **3a**, **4a** and **5a** were absent and there was much unchanged starting material.

Reaction Between the Lithium Enolate of (4S,5R)-4-Methyl-5-phenyl-3-propionyloxazolidin-2-one (1a), Chlorotitanium Triisopropoxide and N-(Benzylidene)toluene-4-sulfonamide. To a solution of **1a** (233 mg, 1 mmol) in ether (6.25 mL) at -78 °C was added 1.5 M LDA (0.73 mL, 1.1 mmol) and the mixture was stirred for 1 h. To this mixture was added chlorotitanium triisopropoxide (0.84 mL, 3.5 mmol) and the mixture was warmed to -46 °C (cyclohexanone / dry ice bath) and stirred for 2 h. The mixture became orange and was then cooled to -78 °C. A solution of *N*-(benzylidene)toluene-4-sulfonamide (519 mg, 2 mmol) in ether-THF (9:1; 7 mL) was added dropwise to the mixture, which was subsequently allowed to warm up to -46 °C and stirred for 2 h. The mixture was allowed to warm to 20 °C, then quenched with saturated aqueous NH_4Cl and extracted with ether (3 x 25 mL). Flash chromatography as before gave **3a** (114 mg, 23 %) and **4a** (137 mg, 28 %).

(2R,3S)-2-Methyl-3-phenyl-3-(N-tosylamino)propionic acid (6a). To a solution of **3a** (246 mg, 0.5 mmol) in THF-water (3:1) (10 mL) at 0 °C were added hydrogen peroxide (0.28 mL of a 30 % wt / vol solution, 2.5 mmol) and lithium hydroxide (53 mg, 1.25 mmol). The mixture was stirred at 0 °C for 3 h and gradually warmed to 20 °C overnight. Excess peroxide was quenched at 0 °C with sodium sulfite (3.8 g) in water (25 mL) and saturated aqueous sodium bicarbonate was added to pH 9-10. THF was removed *in vacuo* and the chiral auxiliary was extracted into CH_2Cl_2 (2 x 40 mL). The aqueous layer was then acidified to pH 1-2 with dilute hydrochloric acid and the carboxylic acid extracted with EtOAc (3 x 60 mL). Drying ($MgSO_4$) and evaporation of the EtOAc layer, then purification by recrystallisation from EtOAc-petrol gave **6a** (118 mg, 71 %) as white crystals, m.p. 135-136 °C. $[\alpha]_D$ -28.1 ° (*c* 1.00 in EtOAc); (Found: C, 61.0; H, 5.6; N, 4.2. $C_{17}H_{19}NO_4S$ requires C, 61.2; H, 5.7; N, 4.2 %); IR (KBr): ν = 3261, 3200-2400 (br), 1709, 1325, 1163 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 1.16 (d, 3 H, *J* = 7.1 Hz, CH_3CH), 2.29 (s, 3 H, Ts-CH_3), 2.88 ('quintet', 1 H, *J* = 7.1 Hz, CH_3CHCH), 4.43-4.57 (br t, 1 H, *J* = 8 Hz, $CHCHNH$), 6.32 (br d, 1 H, *J* = 9 Hz, $CHNH$), 6.98-7.16 (m, 7 H, Ph and Ts-H_2) and 7.44-7.53 (m, 2H, Ts-H_2); MS: *m/z* (%) = 260 (100), 245 (1.1), 178 (3.6), 155 (36.2), 91 (65.0); HRMS: found 260.0733 [calc for $C_{14}H_{14}NO_2S$ (M-$C_3H_5O_2$) 260.0745].

(3R,4S)-3-Methyl-4-phenyl-1-tosylazetidin-2-one (8a). The carboxylic acid **6a** was prepared from **3a** (985 mg, 2 mmol), hydrogen peroxide (1.40 mL, 10 mmol) and lithium hydroxide (210 mg, 5 mmol) as previously described, and was used crude, after base / acid extraction, in the synthesis of the β-lactam **8a**. To a solution of the **6a** in CH_2Cl_2 (20 ml) were added 4-pyrrolidinopyridine (33 mg, 0.22 mmol) and dicyclohexylcarbodiimide (475 mg, 2.3 mmol) and the mixture was stirred at 20 °C overnight. The mixture was then filtered through Celite® and the filtrate was washed with water (2 x 30 mL), 5 % aqueous acetic acid (30 mL) and water (30 mL). Drying ($MgSO_4$) and evaporation of the CH_2Cl_2 layer, then purification by flash chromatography [CH_2Cl_2-petrol (1:1 to 1:0 gradient)] gave **8a** (537 mg, 85 % from **3a**). Recrystallisation from

EtOAc-petrol gave white crystals, m.p. 134-135 °C; $[\alpha]_D$ -114 ° (*c* 1.05 in EtOAc); (Found: C, 64.4; H, 5.5; N, 4.35. $C_{17}H_{17}NO_3S$ requires C, 64.7; H, 5.4; N, 4.4 %); IR (KBr): ν = 1794, 1362, 1169 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 1.34 (d, 3 H, *J* = 7.5 Hz, C*H*$_3$CH), 2.42 (s, 3 H, Ts-CH_3), 3.16 (qd, 1 H, *J* = 7.5 and 3.1 Hz, CH_3C*H*CH), 4.60 (d, 1H, *J* = 3.1 Hz, PhC*H*CH), 7.20-7.37 (m, 7 H, Ph and Ts-H_2) and 7.61-7.66 (m, 2 H, Ts-H_2); MS: *m/z* (%) = 260 (1.0), 197 (1.2), 160 (0.2), 155 (6.0), 132 (0.7), 118 (100), 104 (2.0); HRMS: found 260.0766 [calc for $C_{14}H_{14}NO_2S$ (M-C_3H_3O) 260.0745].

*Preparation of (3*R*,4*R*)-3-Methyl-4-phenyl-1-tosylazetidin-2-one (9a) via (2*R*,3*R*)-2-Methyl-3-phenyl-3-(*N*-tosylamino)propionic acid (7a).* To a solution of **4a** (650 mg, 1.32 mmol) in THF-water (3:1) (12 mL) at 0 °C were added hydrogen peroxide (0.73 mL of a 30 % wt / vol solution, 5.28 mmol) and lithium hydroxide (139 mg, 3.3 mmol). The reaction was then performed as previously described for the preparation of carboxylic acid **6a**, until crude **7a** was isolated. Crude **7a** was then cyclized exactly as described above for crude **6a**. After purification by flash chromatography [CH_2Cl_2-petrol (1:1 to 1:0 gradient)] and recrystallisation from ether-petrol, **9a** was obtained as white crystals (302 mg, 73 % from **4a**), mp 110.5-111.5 °C; $[\alpha]_D$ +212 ° (*c* 1.05 in EtOAc); IR (KBr): ν = 1797, 1362, 1170 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 0.82 (d, 3 H, *J* = 7.6 Hz, C*H*$_3$CH), 2.46 (s, 3 H, Ts-CH_3), 3.60 ('quintet', 1 H, *J* = 7.6 and 6.7 Hz, CH_3C*H*CH), 5.22 (d, 1H, *J* = 6.7 Hz, PhC*H*CH), 7.11-7.35 (m, 7 H, Ph and Ts-H_2) and 7.78-7.83 (m, 2 H, Ts-H_2); MS: *m/z* (%) = 315 (0.2), 260 (4.0), 160 (0.5), 156 (0.6), 132 (0.5), 118 (100), 104 (1.1); HRMS: found 315.0931 [calc for $C_{17}H_{17}NO_3S$ (M^+) 315.0929].

*(3*R*,4*S*)-3-Methyl-4-phenylazetidin-2-one (10a).* A solution of naphthalene (170 mg, 1.33 mmol) in DME (3 mL) was stirred with sodium (26 mg, 1.14 mmol) at 20 °C for 1 h. The resultant emerald-green solution was gradually added to a solution of **8a** (60 mg, 0.19 mol) in DME (3 mL) at -78 °C until a permanent reddish-purple colour developed. After 40 min water (5 mL) was carefully added and the mixture allowed to warm to 20 °C. The mixture was extracted with ether (3 x 20 mL) and the ether layer was dried ($MgSO_4$) and evaporated. Flash chromatography [CH_2Cl_2-petrol (1:1 to 1:0 gradient) then CH_2Cl_2-ether (49:1 to 9:1 gradient)] gave **10a** as a white solid (26 mg, 85 %), m.p. 116-118 °C (lit.[5] 118-120 °C), $[\alpha]_D$ -36.9 ° (*c* 0.96 in $CHCl_3$) [lit.[5] -39.0 ° (*c* 1.0 in $CHCl_3$)]; IR (KBr): ν = 3198, 1755, 1716 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$): δ = 1.43 (d, 3 H, *J* = 7 Hz, C*H*$_3$CH), 3.06 (qd, 1 H, *J* = 7 and 2 Hz, CH_3C*H*CH), 4.31 (d, 1 H, *J* = 2 Hz, PhC*H*CH), 6.2 (br s, 1 H, NH) and 7.36 (s, 5 H, Ph).

*(3*R*,4*R*)-3-Methyl-4-phenylazetidin-2-one (11a).* Repetition of the preceding experiment, but using the *cis*-azetidinone **9a** in place of **8a**, gave **11a** (27 mg, 88 %) as a white solid, m.p. 135-137 °C (lit.[6] 138-140 °C), $[\alpha]_D$ +200 ° (*c* 1.00 in $CHCl_3$) [lit.[6] of antipode -206.7 ° (*c* 1.04 in $CHCl_3$)]; IR (KBr): ν = 3198, 1765, 1717 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$): δ = 0.81 (d, 3 H, *J* = 8 Hz, C*H*$_3$CH), 3.57 (qd, *J* = 8 and 5 Hz, 1 H, CH_3C*H*CH), 4.88 (d, 1 H, *J* = 5 Hz, PhC*H*CH), 6.3 (br s, 1 H, N*H*) and 7.13-7.63 (m, 5 H, Ph).

*(4*S*,5*R*)-4-Methyl-3-[(2*R*,3*S*)-2-methyl-3-phenyl-3-(tosylamino)propionyl]-5-phenyloxazolidin-2-one (3a) from (3*R*,4*S*)-3-Methyl-4-phenyl-1-tosylazetidin-2-one (8a).* To a solution of (4*S*,5*R*)-4-methyl-5-phenyloxazolidin-2-one (46 mg, 0.26 mmol) in THF (1 mL) at -78 °C was added 2.5 M *n*-butyllithium in hexane (114 μL, 0.286 mmol) and the mixture was stirred for 0.5 h. (3*R*,4*S*)-3-Methyl-4-phenyl-1-

tosylazetidin-2-one **8a** (78 mg, 0.25 mmol) in THF (1 mL) was then added and the mixture was gradually allowed to warm to 0 °C and stirred for 4 h. Saturated aqueous ammonium chloride (10 mL) was then added and the mixture extracted with CH_2Cl_2 (3 x 20 mL). Drying ($MgSO_4$) and evaporation of the CH_2Cl_2 layer, followed by purification of the crude material by flash chromatography [CH_2Cl_2-ether (99:1 to 49:1 gradient)] gave **3a** (63 mg, 49 %), which was identified by its ^1H NMR spectrum (80 MHz).

*(4R,5S)-4-Methyl-3-[(2R,3S)-2-methyl-3-phenyl-3-(tosylamino)propionyl]-5-phenyloxazolidin-2-one (ent-**2a**) from (3R,4S)-3-Methyl-4-phenyl-1-tosylazetidin-2-one (**8a**).* This experiment was similar to the preceding preparation of **3a** from **8a**, except that the Li salt of (4*R*,5*S*)-4-methyl-5-phenyloxazolidin-2-one (*ent*-**12**) was used in place of **12** and the reaction was performed on three times the scale to give *ent*-**2a** (303 mg) as a slightly impure (as judged by ^1H NMR spectroscopy) non-crystallizable foam. IR (KBr): ν = 3277, 1778, 1701 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): *inter alia* δ = 0.86 (d, 3 H, *J* = 6.6 Hz, ring -CH_3), 1.08 (d, 3 H, *J* = 6.6 Hz, chain -CH_3), 2.30 (s, 0.15 H, Ts-CH_3 of impurity), 2.33 (s, 3 H, Ts-CH_3), 4.41 ('quintet', 1 H, *J* = 6.6 Hz, chain CH_3CHCH), 4.52 ('t', 1 H, *J* = 8 Hz, $CHCHNH$), 4.67 ('quintet', 1 H, *J* = 6.9 Hz, ring CH_3CHCH), 5.50 (d, 1H, *J* = 7.3 Hz, $PhCHCH$), 5.86 (d, 1 H, *J* = 9.3 Hz, $CHNH$), and 6.94-7.53 (m, 14 H, 2 x Ph and Ts-H_4); MS: *m/z* (%) = 492 (0.3), 337 (6.1), 260 (100), 177 (0.7), 160 (10.9), 156 (2.5), 131 (0.6); HRMS: found 492.1717 [calc for $C_{27}H_{28}N_2O_5S$ (M^+) 492.1719].

*(4R,5S)-4-Methyl-3-[(2R,3R)-2-methyl-3-phenyl-3-(tosylamino)propionyl]-5-phenyloxazolidin-2-one (ent-**5a**) from (3R,4R)-3-Methyl-4-phenylazetidin-2-one (**9a**).* This experiment was similar to the preparation of *ent*-**2a** from **8a**. Yield of *ent*-**5a** was 204 mg (53 %), m.p. 153-154 °C; $[\alpha]_D$ -51.5 ° (*c* 1.01 in EtOAc); IR (KBr): ν = 3264, 1795, 1687 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 0.86 (d, 3 H, *J* = 6.6 Hz, ring -CH_3), 1.15 (d, 3 H, *J* = 6.9 Hz, chain -CH_3), 2.31 (s, 3 H, Ts-CH_3), 4.27 ('quintet', 1 H, *J* = 6.8 Hz, chain CH_3CHCH), 4.48 ('quintet', 1 H, *J* = 6.8 Hz, ring CH_3CHCH), 4.84 (dd, 1 H, *J* = 9.4 and 6.7 Hz, $CHCHNH$), 5.37 (d, 1 H, *J* = 7.1 Hz, ring $PhCHCH$), 5.43 (d, 1 H, *J* = 9.4 Hz, $CHNH$) and 7.01-7.60 (m, 14 H, 2 x Ph and Ts-H_4); MS: *m/z* (%) = 337 (0.6), 260 (100), 233 (0.2), 160 (1.0), 155 (26.5), 131 (0.2); HRMS: found 337.1562 [calc for $C_{20}H_{21}N_2O_3$ (M-$C_7H_7O_2S$) 337.1552].

*Reaction Between N-(Benzylidene)toluene-4-sulfonamide and the Enolate from (4S,5R)-3-Butyryl-4-methyl-5-phenyloxazolidin-2-one (**1b**), Titanium (IV) Chloride and Diisopropylethylamine.* The *N*-butyryloxazolidinone **1b** (247 mg, 1 mmol) and *N*-(benzylidene)toluene-4-sulfonamide were subjected to a $TiCl_4$-mediated reaction at -55 °C as previously described for the *N*-propionyloxazolidinone **1a**. An 80 MHz ^1H NMR spectrum of the crude product was consistent with the formation of two main diastereomers **3b** and **4b** in a 6:1 ratio. Flash chromatography gave the major product *(4S,5R)-4-methyl-3-[(2R,3S)-2-ethyl-3-phenyl-3-(tosylamino)propionyl]-5-phenyloxazolidin-2-one* (**3b**) (376 mg, 74 %) as a slightly impure (as judged by ^1H NMR) white foam, which could not be crystallized and which had the following properties: $[\alpha]_D$ -83.1 ° (*c* 1.17 in EtOAc); IR (KBr): ν = 3284, 1775, 1700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): *inter alia* δ = 0.78 (d, 3 H, *J* = 6.6 Hz, ring-CH_3), 0.87 (t, 3 H, *J* = 7.4 Hz, CH_2CH_3), 1.23-1.43 (m, 1 H, 1/2 x $CHCH_2CH_3$), 1.66-1.86 (m, 1 H, 1/2 x $CHCH_2CH_3$), 2.28 (s, 3 H, Ts-CH_3), 2.42 (s, 0.15 H, Ts-CH_3 of impurity), 4.23-4.32 (m, 1 H, CH_2CHCH), 4.59 (dd, 1 H, *J* = 10.0 and 8.3 Hz, $CHCHNH$), 4.74 ('quintet', 1 H, *J* = 6.8 Hz, ring $CHCHCH_3$), 5.62 (d, 1 H, *J* = 7.1 Hz, $PhCHCH$), 6.00 (d, 1 H, *J* = 10 Hz, $CHNH$) and

6.93-7.48 (m, 14 H, 2 x Ph and Ts-H_4); MS: *m/z* (%) = 351 (5), 260 (100), 247 (6), 232 (2), 174 (10), 155 (35) 131 (2); HRMS: found 351.1709 [calc for $C_{21}H_{23}N_2O_3$ (M-$C_7H_7O_2S$) 351.1709]. The minor product, thought to be **4b**, could not be separated chromatographically from the small amount of toluene-4-sulfonamide formed in the reaction.

(3R,4S)-3-Ethyl-4-phenyl-1-tosylazetidin-2-one (8b). This was prepared from **3b** (306 mg, 0.88 mmol) by analogy with the conversion of **3a** to **8a**. Recrystallisation from EtOAc-petrol gave the *title compound* **8b** (206 mg, 71 %) as white crystals, m.p. 88-89 °C; $[\alpha]_D$ -132 ° (*c* 1.08 in EtOAc); (Found: C, 65.6; H, 5.8; N, 4.2. $C_{18}H_{19}NO_3S$ requires C, 65.6; H, 5.8; N, 4.25 %); IR (KBr): ν = 1795, 1360, 1169 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 0.96 (t, 3 H, *J* = 7.4 Hz, CH_3CH_2), 1.64-1.91 (m, 2 H, CH_2), 2.42 (s, 3 H, Ts-CH_3), 3.08 (ddd, 1 H, *J* = 8.1, 6.6 and 3.1 Hz, CH_2CHCH), 4.69 (d, 1H, *J* = 3.1 Hz, PhC*H*CH), 7.20-7.34 (m, 7 H, Ph and Ts-H_2) and 7.63-7.67 (m, 2 H, Ts-H_2); MS: *m/z* (%) = 260 (3), 197 (4), 155 (11) and 132 (100); HRMS: found 260.0750 [calc for $C_{14}H_{14}NO_2S$ (M-C_4H_5O) 260.0745].

Reaction Between N-(Benzylidene)toluene-4-sulfonamide and the Enolate from (4S,5R)-4-Methyl-5-phenyl-3-phenylacetyloxazolidin-2-one (1c), Titanium (IV) Chloride and Diisopropylethylamine. The *N*-phenylacetyloxazolidinone **1c** (295 mg, 1 mmol) and *N*-(benzylidene)toluene-4-sulfonamide were subjected to a $TiCl_4$ -mediated reaction at -55 °C as previously described for the *N*-propionyloxazolidinone **1a**. An 80 MHz ^1H NMR spectrum of the crude product was consistent with the formation of two main diastereomers **4c** and **3c** in a 2.8:1 ratio. Flash chromatography [gradient from CH_2Cl_2 to CH_2Cl_2-Et_2O (98:2)] first gave the minor product (4*S*,5*R*)-3-[(2*R*,3*S*)-2,3-diphenyl-3-(tosylamino)propionyl]-4-methyl-5-phenyloxazolidin-2-one (**3c**) (135 mg, 24%) as a non-crystallizable solid which had the following properties: $[\alpha]_D$ -1.8 ° (*c* 1.02 in $CHCl_3$); IR (KBr): ν = 3277, 1777, 1703 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 0.83 (d, 3 H, *J* = 6.6 Hz, $CHCH_3$), 2.26 (s, 3 H, Ts-CH_3), 4.68 ('quintet', 1 H, *J* = 6.8 Hz, CH_3CHCH), 4.97 (dd, 1 H, *J* = 10.0 and 8.5 Hz, CHCHNH), 5.51 (d, 1 H, *J* = 7.1 Hz, PhCHCHCH$_3$), 5.63 (d, 1 H, *J* = 8.5 Hz, PhCHCHNH), 6.02 (d, 1 H, *J* = 10 Hz, CHNH) and 6.88-7.45 (m, 19 H, 3 x Ph and Ts-H_4); MS: *m/z* (%) = 421 (0.2), 383 (0.1), 338 (0.2), 295 (62), 260 (51) and 91 (100); HRMS: found 383.1520 [calc for $C_{25}H_{21}NO_3$ (M-$TsNH_2$) 383.1521].

The major product, (4*S*,5*R*)-3-[(2*R*,3*R*)-2,3-diphenyl-3-(tosylamino)propionyl]-4-methyl-5-phenyloxazolidin-2-one (**4b**) (377 mg, 68 %) eluted afterwards and was recrystallised from $CHCl_3$-petrol to give fluffy, white crystals with the following properties: m.p. 237-238 °C. $[\alpha]_D$ +51.9 ° (*c* 1.06 in $CHCl_3$); (Found: C, 64.9; H, 5.2; N, 4.5. $C_{32}H_{30}N_2O_5S.1/3CHCl_3$ requires C, 65.3; H, 5.1; N, 4.7 %); IR (KBr): ν = 3333, 1770, 1685 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 0.20 (d, 3 H, *J* = 6.6 Hz, $CHCH_3$), 2.36 (s, 3 H, Ts-CH_3), 4.44 ('quintet', 1 H, *J* = 6.7 Hz, CH_3CHCH), 4.63 (br d, 1 H, *J* = 4.9 Hz, NH), 4.98 (dd, 1 H, *J* = 10.9 and 4.9 Hz, CHCHNH), 5.37 (d, 1 H, *J* = 7.3 Hz, PhCHCHCH$_3$), 5.71 (d, 1 H, *J* = 10.9 Hz, PhCHCHNH) and 7.00-7.49 (m, 19 H, 3 x Ph and Ts-H_4); MS: *m/z* (%) = 383 (3), 338 (3), 295 (84), 260 (65), 177 (8) and 118 (100); HRMS: found 383.1519 [calc for $C_{25}H_{21}NO_3$ (M-$TsNH_2$) 383.1521].

A Ti-mediated reaction was performed similarly to the preceding experiment, but at -78 °C rather than -55 °C. The crude product was examined by 80 MHz ^1H NMR spectroscopy and found to contain **4c** and **3c** in the ratio 3.3:1. Flash chromatography gave **3c** (125 mg, 22.5 %) followed by **4c** (408 mg, 74 %).

Attempted Epimerization of (4S,5R)-3-[(2R,3S)-2,3-diphenyl-3-(tosylamino)propionyl]-4-methyl-5-phenyloxazolidin-2-one (3c). To a solution of $TiCl_4$ (48 μL, 0.44 mmol) in CH_2Cl_2 (0.28 mL) was added EtN^iPr_2 (84 μL, 0.48 mmol). The mixture was stirred for 10 min and then cooled to -55 °C. A solution of **3c** (221 mg, 0.4 mmol) in CH_2Cl_2 was then added and the mixture was stirred for 3.5 h. The mixture was then quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give unchanged **3c** (218 mg, 99 %), as judged by NMR and tlc.

Attempted Epimerization of (4S,5R)-3-[(2R,3R)-2,3-Diphenyl-3-(tosylamino)propionyl]-4-methyl-5-phenyloxazolidin-2-one (4c). The preceding experiment was repeated using **4c**, which was also unchanged (100% recovery).

Conversion of 3c to (3R,4S)-3,4-Diphenyl-1-tosylazetidin-2-one (8c). This was performed using **3c** (114 mg, 0.21 mmol), by analogy with the conversion of **3a** to **8a**. Flash chromatography [CH_2Cl_2-petrol (1:1 to 1:0 gradient)] gave the *title compound* **8c** (60 mg, 77 %), which after crystallisation from ether-petrol was obtained as white crystals, m.p. 123-124 °C; $[\alpha]_D$ -28.5 ° (*c* 0.96 in EtOAc); IR (KBr): ν = 1781, 1363, 1166 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 2.45 (s, 3 H, Ts-CH_3), 4.27 (d, 1 H, *J* = 3.4 Hz, PhC*H*), 4.99 (d, 1H, *J* = 3.4 Hz, PhC*H*), 7.02-7.12 (m, 2 H, Ph-H_2), 7.26-7.41 (m, 10 H, Ar-H_{10}) and 7.70-7.75 (m, 2 H, Ts-H_2); MS: *m/z*(%) = 222 (1), 180 (100), 118 (10); HRMS: found 222.0894 [calc for $C_{15}H_{12}NO$ (M^+-Ts) 222.0919]

*Conversion of 4c to (3S,4R)-3,4-Diphenyl-1-tosylazetidin-2-one (*ent-*8c) and (3R,4R)-3,4-Diphenyl-1-tosylazetidin-2-one (9c).* This was performed using **4c** (240 mg, 0.43 mmol), by analogy with the conversion of **3a** to **8a**. Flash chromatography [CH_2Cl_2-petrol (1:1 to 1:0 gradient)] gave a mixture of *ent*-**8c** and **9c** (148 mg, 91 %) which gave two closely running spots on tlc [CH_2Cl_2-Et_2O (49:1) as eluant]. Recrystallisation of this mixture from ether-petrol gave *ent*-**8c** (98 mg, 60 %), mp 123-124 °C; $[\alpha]_D$ +28.7 ° (*c* 0.97 in EtOAc); (Found: C, 69.6; H, 5.25; N, 3.65. $C_{22}H_{19}NO_3S$ requires C, 70.0; H, 5.1; N, 3.7 %); IR and ^1H NMR (250 MHz, $CDCl_3$): identical to those of **8c**. The mother liquor from the crystallisation was rechromatographed to yield a further quantity of *ent*-**8c** (38 mg, 23 %) [total isolated yield of *ent*-**8c** = 83 %]. A small amount (9 mg, 5.5 %) of material enriched in **9c** was also obtained [(**9c**: *ent*-**8c** ratio = 4.4:1, as judged by ^1H NMR (250 MHz, $CDCl_3$): *inter alia* δ = 2.46 (s, 3 H, Ts-CH_3), 4.93 (d, 1 H, *J* = 6.9 Hz, PhC*H*), 5.48 (d, 1H, *J* = 6.9 Hz, PhC*H*), 6.85-7.37 (m, 12 H, 2 x Ph and Ts-H_2) and 7.78-7.83 (m, 2 H, Ts-H_2)]. Treatment of a solution of this mixture (9 mg, 0.024 mmol) in $CDCl_3$ (0.5 mL) with triethylamine (3.5 μL, 0.025 mmol) for 4 h at room temperature gave a 1:7 ratio of **9c**:*ent*-**8c**, as judged by ^1H NMR spectroscopy.

Attempted Reductive Cleavage of the Chiral Auxiliary from (4S,5R)-3-[(2R,3S)-2,3-Diphenyl-3-(tosylamino)propionyl]-4-methyl-5-phenyloxazolidin-2-one (3c) using $LiBH_4$. To a solution of **3c** (554 mg, 1 mmol) in THF (10 mL) at 0 °C was added $LiBH_4$ (110 mg, 5 mmol). The mixture was strirred at 0 °C for 2.5 h, then saturated aqueous NH_4Cl (10 mL) was added and the mixture was extracted with ether (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$), evaporated and subjected to flash chromatography [CH_2Cl_2-petrol (1:1 to 1:0 gradient)], whereupon *N*-benzyltoluene-4-sulfonamide (**15**) (221 mg, 85 %) was

obtained and was identified by its ^1H NMR spectrum. After crystallisation from CH_2Cl_2-petrol this product had m.p. 116-117 °C (lit.[33] 116 °C).

Attempted Reductive Cleavage of the Chiral Auxiliary from (4S,5R)-3-[(2R,3R)-2,3-Diphenyl-3-(tosylamino)propionyl]-4-methyl-5-phenyloxazolidin-2-one (4c) using $LiBH_4$. This experiment was conducted using **4c** to replace **3c** in the preceding experiment, but the reaction time was 24 h. Again *N*-benzyltoluene-4-sulfonamide (**15**) (71 %) was isolated.

X-Ray Crystallography

Data for a single crystal of **9a** were recorded with a CAD4 diffractometer using the program ***CAD4/PC***;[34] 1176 independent reflections were collected. The structure of **9a** was solved by direct methods using ***SHELXS86***[35] and refined on F^2 by full motion least squares techniques using ***SHELXL93***.[21] All atoms were refined isotropically, except O and S atoms. H atoms were placed at calculated positions by using the *AFIX* command in ***SHELXL93***. Displacement parameters of H atoms were kept fixed at the isotropic values of parent atoms. Absolute configuration was confirmed by Flack factor[36] in ***SHELXL93***, x = -0.5(5); for the enantiomeric structure x = 1.5(5). Molecular graphics were generated using ***PLUTON-94***.[37]

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