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Electrophilic amination of enolates with oxaziridines: effects of oxaziridine structure and reaction conditions

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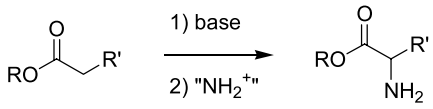
Abstract—A range of *N*-alkoxycarbonyl- and *N*-carboxamido-oxaziridines has been prepared to test the effects of oxaziridine structure on yields of enolate amination product. Side-products arising from reaction of aldehyde-derived oxaziridines with base were identified, while a ketone-derived oxaziridine afforded moderate yields of amination product with stabilised carbanions.

1. Introduction

The electrophilic amination of enolates provides a conceptually simple and powerful approach to α-amino carbonyl compounds, important structural motifs in many biologically significant molecules (Scheme 1).[1] A variety of useful reagents have been developed for this reaction, including haloamines, hydroxylamine derivatives, azides, nitroso compounds and azodicarboxylates.[1a] However, there are currently limitations or drawbacks to all of these reagents, as some (e.g., haloamines, hydroxylamine derivatives) give only moderate yields and have limited scope,[1a] whilst others (azides, nitroso compounds, azodicarboxylates) require additional synthetic manipulations of the initial product in order to obtain the desired α-amino carbonyl compound. Very few directly deliver nitrogen bearing a synthetically useful protecting group.[1a,c]



Scheme 1.

Oxaziridines are well known as electrophilic oxidising agents and in particular *N*-sulfonyl oxaziridines have been widely exploited for the oxidation of a variety of nucleophiles.[2] However, structural modification of the oxaziridine, most notably the nitrogen substituent, can result in useful reagents for the electrophilic amination of nucleophiles. Indeed a number of examples of oxaziridine-mediated enolate amination have been reported. The use of *N*–H oxaziridines in this reaction was first described by Schmitz[3] for a limited range of highly stabilised enolates. This chemistry was recently further developed by Page, who reported asymmetric amination of enolates using enantiopure camphoryl or fenchyl *N*–H oxaziridines.[4] Good yields and moderate stereoselectivity were obtained in some cases, but the reaction was rather substrate-specific. In addition, ester and nitrile units in the substrate were usually hydrolysed (and in some cases decarboxylated). Collet and co-workers have demonstrated that *N*-alkoxycarbonyl oxaziridines (e.g., **1**) can also be used to aminate enolates, although the yields were low due to competing aldol reaction with the aldehyde co-product (Scheme 2).[5] Asymmetric variants of this work have been published by Enders,[6] using enantiopure α-silylketones, and by our group, using *N*-menthyloxycarbonyl oxaziridine **2**, albeit with low to moderate levels of stereoselectivity.[7] In addition, preliminary results in our group indicated that the aldol side reaction could be minimised by incorporation of an *ortho*-cyano group on the aromatic 3-substituent of *N*-carboxamido-oxaziridines **3**.[8]

In view of the extremely high synthetic value of the enolate amination process, we considered that attempts to improve the reaction yields by variation of oxaziridine structure and the reaction conditions would be a very worthwhile endeavour. In this paper, we report our efforts in this area,

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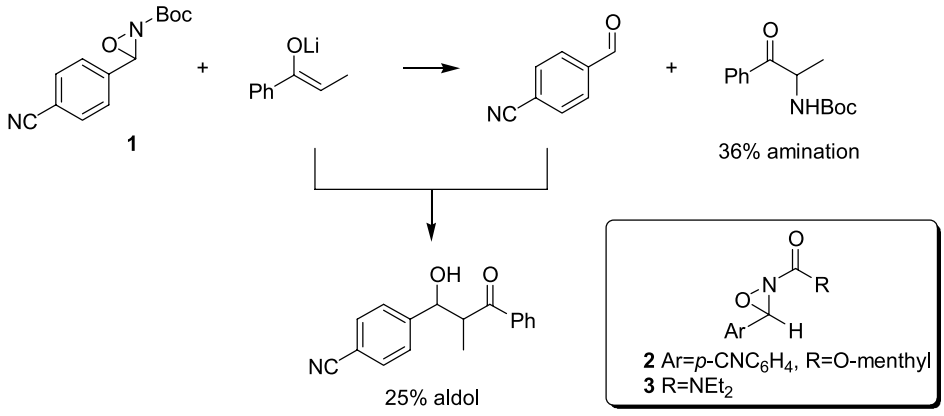


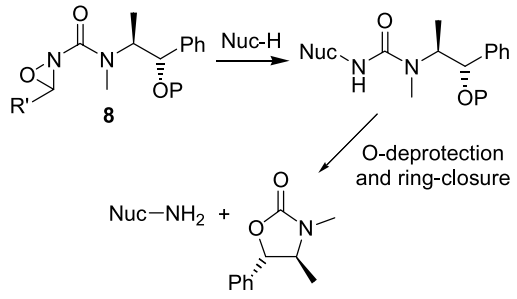
Scheme 2.

including the synthesis of several novel *N*-alkoxycarbonyl- and *N*-carboxamido-oxaziridines for this purpose.

2. Results and discussion

2.1. Oxaziridine synthesis

Our aforementioned earlier work had indicated that structural modification of the oxaziridine offered a means to improve the efficiency of amination. In order to probe these effects more deeply, a range of reagents **3**–**8** (Fig. 1) was synthesised, based on the *N*-alkoxycarbonyl- and *N*-carboxamido-oxaziridines **1** and **3**. The *o*-cyanophenyl substituted oxaziridine **3b** was of particular interest for further study as it had shown promise for reducing the amount of aldol side reaction,[8] and the *p*-chlorophenyl analogue **3a** was prepared for comparison purposes. A separate study had shown that the 3,3-disubstituted oxaziridine **4** was a highly efficient reagent for amination of sulfides,[9] and it was anticipated that it may also prove useful for amination of enolates. The ultimate aim of this research was to develop reagent-controlled asymmetric amination, and although the ester groups of oxaziridine **4** provide a useful handle for introduction of chirality, chiral analogues of this reagent would be likely to give low stereoselectivity as the ring carbon is not a stereocentre. Other non-identically 3,3-disubstituted oxaziridines **5** and **6**, and a mono-ester substituted oxaziridine **7**, were therefore targeted. In addition, a pseudoephedrine-derived oxaziridine **8** was synthesised in an attempt to address the main drawback of *N*-carboxamido-oxaziridines, namely that the aminated products contain a urea linkage that is potentially difficult to cleave. It was proposed that this auxiliary might enable cleavage of the urea via intramolecular nucleophilic attack of the hydroxyl group (Scheme 3). This auxiliary would also allow further investigation of asymmetric enolate amination. It was envisaged that the poor stereoinduction obtained with menthyloxycarbonyl oxaziridine **2**[7] could be improved by using enantiopure *N*-carboxamido-oxaziridines such as **8**, due to increased conformational restriction about the *N*-carbonyl bond relative to the *O*-carbonyl bond in **2**.



Scheme 3.

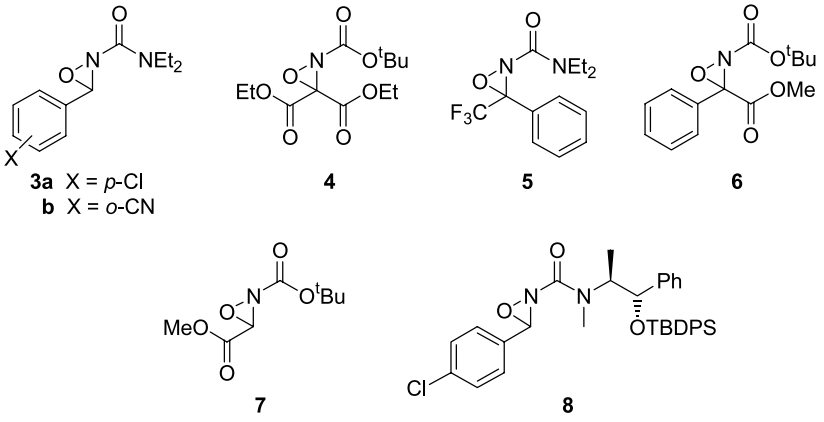
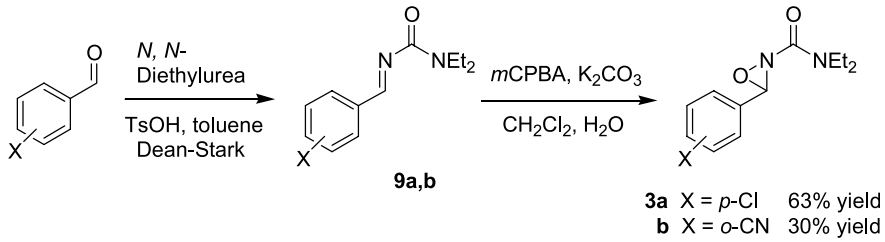


Figure 1.

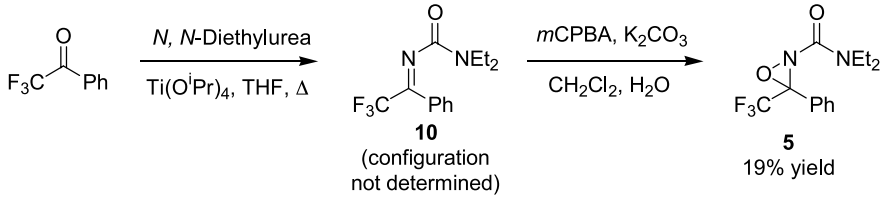


Scheme 4.

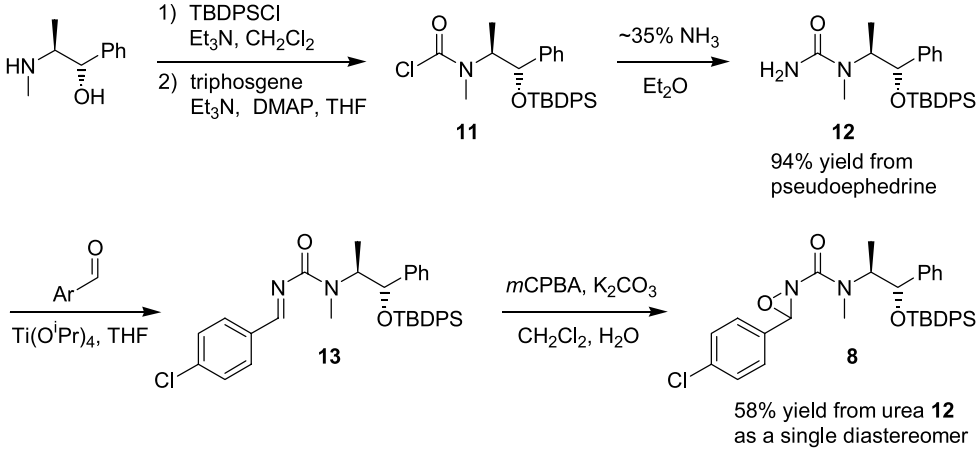
Synthesis of the requisite *N*-carboxamido-oxaziridines **3** was achieved by direct condensation of the appropriate urea and carbonyl compound, followed by oxidation of the resulting imines **9** (Scheme 4). For the imine oxidation, we preferred to use *m*CPBA/K_2CO_3 rather than the experimentally less convenient *m*CPBA/BuLi protocol employed in our preliminary work.[8] The TsOH-catalysed condensation failed to provide other *N*-carboxamido-imines **10** and **13**, required for synthesis of oxaziridines **5** and **8**, respectively, but a milder approach utilising titanium (IV) isopropoxide as a Lewis acid catalyst and water scavenger proved successful (Schemes 5 and 6). This procedure had previously only been reported for in situ formation of imines, as part of a reductive amination.[10]

The ketomalonate-derived oxaziridine **4** was prepared according to the published procedure,[9] involving an aza-Wittig imine synthesis. This approach is suitable for many *N*-alkoxycarbonylimines, but for unstable compounds the high temperatures required can prove too harsh. An alternative approach, involving elimination from an α-bromo amine, has been reported for a variety of unstable imines,[11] and is attractive as the reaction can be carried out at low temperature and the imine purified by simple filtration to remove $Et_3N{\cdot}HBr$. This procedure is particularly suitable for making α-carbonyl imines, such as **16** and **18**, as these can then be derived from readily available and inexpensive amino acid derivatives (Schemes 7 and 8). The bromide **15** required for synthesis of methyl glycinate-derived oxaziridine **7** was prepared from glycine derivative **14** (Scheme 7). Subsequent elimination with triethylamine was achieved at low temperature and the cold crude imine **16** rapidly transferred and filtered via cannula and sinter into a pre-prepared *m*CPBA/*n*-BuLi solution. The yield of oxaziridine **7** was extremely low, presumably due to the inefficiency of the transfer/filtration procedure, which allowed the sensitive imine to warm considerably above −78 °C. Some attempts were made to improve the yield of this route, but this was hindered due to the bromide and imine intermediates being unstable (the imine in particular could not be detected at room temperature). It was envisaged that a one-pot elimination–oxidation might be possible, with the basic conditions required for oxidation potentially also carrying out the elimination. However treatment of the bromide **15** with 2.5 equiv of *m*CPBA/*n*-BuLi solution failed to deliver any oxaziridine. Other attempts including the use of anhydrous K_2CO_3 with subsequent addition of *m*CPBA were also unsuccessful.

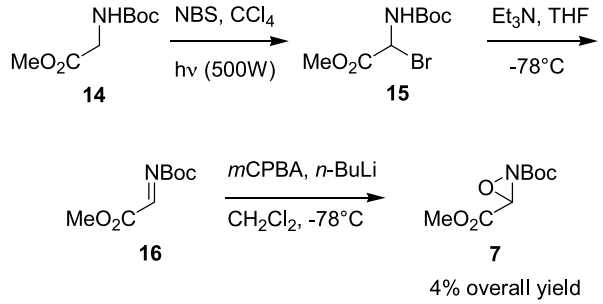
The same approach was utilised for synthesis of the methyl phenylglycinate-derived oxaziridine **6** (Scheme 8). In this



Scheme 5.



Scheme 6.



Scheme 7.

case the imine **18** proved to be significantly more stable and could be purified by silica chromatography. In fact the imine was formed directly from *N*-BOC methyl phenylglycinate **17** in the bromination reaction. The reaction afforded a 5:3 mixture of imine and starting material, with approximately quantitative yield based on recovered starting material, and although no attempts were made to optimise this reaction it is likely that the yield could be improved by extension of the reaction time and/or addition of extra NBS. Oxidation using the simple *m*CPBA/K_2CO_3 procedure afforded the oxaziridine **6** in high yield.

2.2. Structural information

N-Alkoxycarbonyl and *N*-carboxamido-oxaziridines having two different ring carbon substituents exist as equilibrium mixtures of cis and trans isomers, which can interconvert by inversion at nitrogen (e.g., $\Delta G^{\ddagger} = 18.3$ kcal mol^{-1} for oxaziridine **1**).[5] This process is slow on the NMR timescale, such that distinct signals can be observed for the two isomers. The cis–trans ratio depends on the relative steric influence of the two carbon substituents, and if there is a large difference in size the oxaziridine can exist exclusively in the trans form. In these cases, the nitrogen atom is in effect thermodynamically configurationally stable, with its configuration directly determined by that of the ring carbon stereocentre. This is clearly of significance when attempting asymmetric amination using chiral oxaziridines.

The cis–trans ratios of oxaziridines **3**–**8** are shown in Table 1. Clearly oxaziridine **4** can only exist as one isomer, but oxaziridines **3a** and **3b** are also observed in almost exclusively one isomeric form (presumably trans) in solution. A single stereoisomer was also observed in the ^{1}H and ^{19}F NMR spectra of oxaziridine **5**. X-ray crystallography showed the carboxamido and trifluoromethyl groups *trans* to each other (Fig. 2), and this is presumably also the form present in solution. In contrast, mixtures of isomers were observed for oxaziridines **6** and (surprisingly) **7** with the major isomer presumably as shown. The ^{1}H NMR spectrum of pseudoephedrine-derived oxaziridine **8** also showed two sets of resonances in a 2:1 ratio (in $CDCl_3$), but for this reagent there are three potential causes of the isomerism: invertomers (cis–trans isomers), rotamers (about the exocyclic nitrogen–carbonyl bond) and diastereomers (two possible configurations of the ring carbon). Comparison with the other aldehyde-derived *N*-carboxamido-oxaziridines (>98:2 ratio) suggests that the observed 2:1 ratio is unlikely to be caused by invertomers. Diastereomers were also ruled out as the isomeric ratio was found to be dependent on solvent, changing to a 1:1 ratio in toluene-d_6. This therefore indicated that the isomerism was due to rotamers, and that the oxaziridine **8** was formed as a single diastereomer, the relative configuration of which was not assigned.

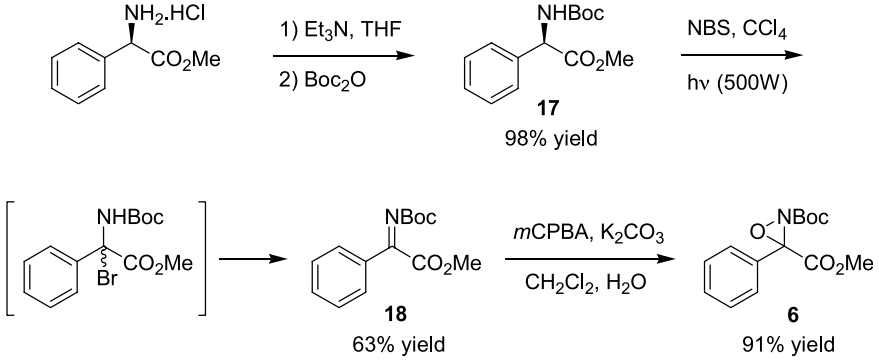
Table 1. cis–trans isomerism of oxaziridines

Entry	Oxaziridine	trans:cis[a]
1	**3a**	>98:2
2	**3b**	>98:2
3	**4**	—
4	**5**	>98:2
5	**6**	71:29
6	**7**	69:31
7	**8**	>98:2

[a] Ratio determined by integration of peaks in the ^{1}H NMR spectrum.

2.3. Amination of *t*-butyl acetate

With several oxaziridines in hand, we were particularly interested in investigating their use in amination of ester enolates, since this would lead to a direct synthesis of protected amino acids. Preliminary results had suggested that the *o*-cyanophenyl substituted oxaziridine **3b** could virtually eliminate formation of the aldol product on amination of *t*-butyl acetate.[8] Thus addition of **3b** to the enolate derived from *t*-butyl acetate and LDA at −78 °C, followed by gradual warming to room temperature prior to quenching and work-up was reported to afford 55% yield of α-amino ester **19** and only 7% yield of aldol product **20b**. However, in further investigations we found difficulty in obtaining such high yields of **19**, and discovered that the nature of the aqueous work-up for this reaction was crucial:



Scheme 8.

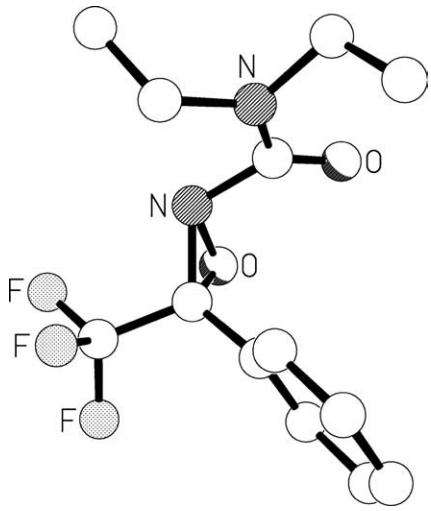
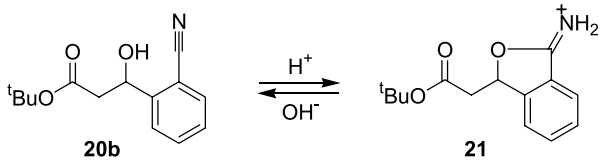


Figure 2. X-ray crystal structure of oxaziridine **5**.

the observed amount of aldol product was low only when an aqueous acid work-up was used. When the reaction was repeated and the acid wash omitted from the work-up procedure, a 1:1 ratio of α-amino ester **19** and aldol product **20b** was observed in the ^{1}H NMR spectrum of the crude product and 33% isolated yield of α-amino ester **19** was obtained (Scheme 9). This was comparable to the result obtained with the *p*-chlorophenyl substituted oxaziridine **3a**, which produced a 4:3 ratio of α-amino ester **19** and aldol product **20a**, with 24% yield of the α-amino ester **19**. Therefore, the *ortho*-cyano substituent in **3b** does not appear significantly to affect the ratio of **19**:**20** in the amination reaction.

Further study of the reaction involving oxaziridine **3b** indicated that the aldol product **20b** had been extracted into the acidic aqueous layer during work-up of the original experiment, and that this compound could in fact be recovered by basifying the aqueous layer with saturated aqueous $NaHCO_3$ (to pH∼8), followed by extraction with dichloromethane. A possible explanation for the acid-mediated removal of the aldol product **20b** could involve reversible formation of a cyclic imino ether **21** via intramolecular nucleophilic attack of the hydroxyl group on the *ortho*-cyano substituent (Scheme 10). This compound is likely to be sufficiently basic to be protonated by 1 M HCl, causing it to be washed into the aqueous layer (pK_a values:[12] HCl = −2.2; PhC(OH)(=NH_2^+) = −2.0). On neutralisation this could undergo the reverse reaction,



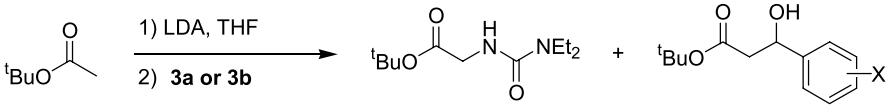
20b **21**

Scheme 10.

regenerating **20b**. When the corresponding *p*-cyanobenzaldehyde aldol product (prepared from the reaction of the enolate of *tert*-butyl acetate with *p*-cyanobenzaldehyde) was subjected to the same work-up procedure, no washing out was observed, supporting involvement of this intramolecular interaction of the hydroxyl and *ortho*-cyano groups.

It therefore appears that the *ortho*-substituent actually has little or no effect in preventing the aldol reaction, although it may be useful in allowing easy separation of the amination and aldol products. In order to further probe the effect of oxaziridine substituents on the yield of amination product, other oxaziridines were also tested with the enolate derived from *t*-butylacetate and LDA. These proved even less successful than **3**. Thus, 3-phenyltrifluoromethyloxaziridine **5** (11% **19** along with significant amounts of iminoaldol product and unreacted **5** in the ^{1}H NMR spectrum of the crude mixture) gave lower yields than **3**, while 3-alkoxycarbonyl oxaziridines **6** and **7** gave no observable amination product. Yields were also low with ketomalonate-derived oxaziridine **4**.

In view of the disappointing lack of improvement on changing the oxaziridine, we decided to focus on modification of the reaction conditions. The *p*-chlorophenyl substituted oxaziridine **3a**, which could be synthesised in high yield from inexpensive starting materials, was selected for further study (Table 2). Use of LiHMDS as base gave a very similar result to the above reaction using LDA. A∼1:1 crude ratio of amination and aldol products (**19** and **20a**) was formed, with 22% yield of amination (entry 2). Switching to NaHMDS had a significant effect on the reaction (entries 3–5). With 1 equiv of oxaziridine very little amination was observed (entry 3), but 2 equiv gave 30% yield of α-amino ester **19** with very little aldol product **20a** detectable (entry 4). Use of 3 equiv of oxaziridine had no extra benefit, again giving 30% yield of amination product (entry 5). Potassium and magnesium counterions did not have the same effect. Use of KHMDS with 2 equiv of oxaziridine **3a** afforded a 1:1 ratio of amination and aldol

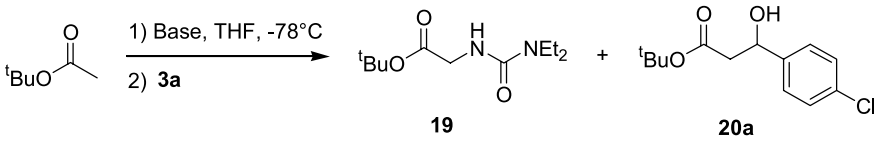


19 **20a** X = *p*-Cl
b X = *o*-CN

Oxaziridine **3a** -> ~4:3 **19** : **20a**; 24% yield **19**.
Oxaziridine **3b** -> ~1:1 **19** : **20b**; 33% yield **19**.

Scheme 9.

Table 2.



Entry	Base[a]	**19**/**20a**[b]	Yield of **19**[c] (%)
1	LDA	4:3	24
2	LiHMDS	1:1	22
3	NaHMDS	—	<5
4	NaHMDS (2 equiv **3a**)	<5% **20a**	30
5	NaHMDS (3 equiv **3a**)	<5% **20a**	30
6	KHMDS (2 equiv **3a**)	1:1	n.d.
7	LDA/$MgBr_2$	1:1	11
8	^{t}BuLi	1:1	15

[a] Using 1 equiv of base, *t*-butyl acetate and oxaziridine **3a** unless otherwise stated.
[b] Approximate ratio measured by integration of the (C=O)CH_2 peaks in the ^{1}H NMR spectrum of the crude product.
[c] Yield based on *t*-butyl acetate.

products, but only in low yield (entry 6), and a similar result was observed for the magnesium enolate, formed by transmetallation of the lithium enolate with magnesium bromide (entry 7). The effect of using non-amide bases was also studied, but deprotonation with ^{t}BuLi produced the same 1:1 ratio of amination and aldol products, and in lower yield than LDA (entry 8). In addition to the results in Table 2, the use of sodium hydride, sodium *t*-butoxide and butylmagnesium diisopropylamide was studied, but these bases resulted in little or no observable amination product being formed.

The observation that NaHMDS gave only trace amounts of aldol product suggests that the mechanism may involve an intermediate hemiaminal **22** that is stabilised by the sodium counterion (Scheme 11). This explanation is analogous to that proposed for α-hydroxylation using *N*-sulfonyl oxaziridines, in which formation of the imino-aldol product could be minimised by using sodium or potassium counterions (Scheme 11).[13]

The reason that 2 equiv of oxaziridine were required in order to obtain any α-amino ester **19** when using NaHMDS was initially not clear. Presumably, the first equivalent of oxaziridine was consumed by side reactions and the second then underwent the amination reaction to some extent. A more detailed analysis of this reaction and its side products was carried out in order to clarify the process. This revealed that amide **23** was formed in ~19% yield based on oxaziridine, along with an imino-aldol product **24** which was detected in the crude mixture in a ~3:1 ratio of **19**:**24** based on integration of the (C=O)CH_2 peaks in the ^{1}H NMR spectrum (Fig. 3).

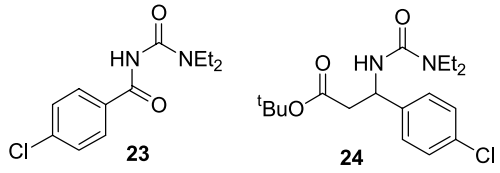
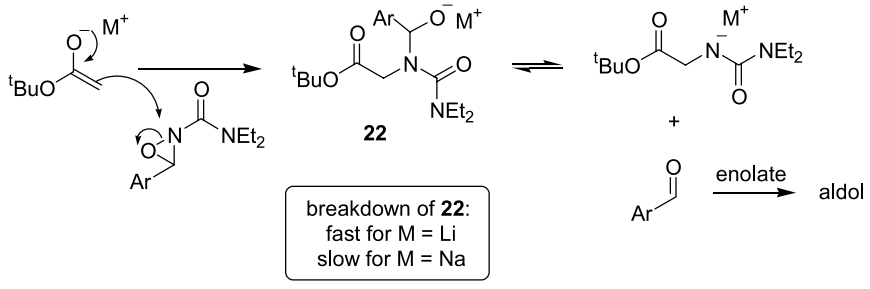
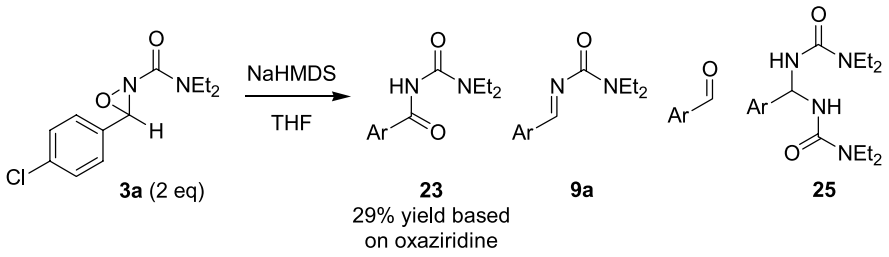


Figure 3.

It had previously been reported that ring deprotonation of oxaziridines could afford amide products[14] so the production of amide **23** in the amination reaction suggested that this process could be occurring here. This could have been carried out by the enolate, but also possibly by NaHMDS, which may have been present in the reaction mixture due to incomplete or reversible[15] deprotonation of the ester (pK_a of *t*-butyl acetate in DMSO=30.3; pK_a of HMDS in DMSO=30)[16]. In order to test this theory, direct reaction of oxaziridine **3a** and NaHMDS was carried out. Reaction of 3 equiv of oxaziridine with NaHMDS in THF at −78 °C demonstrated that approximately 2 equiv were consumed by the base to produce a mixture of amide **23**, imine **9a**, *p*-chlorobenzaldehyde and diaminal **25**. A preparative repeat of this reaction using 2 equiv of oxaziridine and



Scheme 11.



Scheme 12.

allowing the reaction to warm to room temperature before quenching, as in the amination procedure, afforded 29% yield of the amide **23** (Scheme 12). It is significant that oxaziridine **3a** reacts with NaHMDS at −78 °C, as no reaction of this oxaziridine with the enolate derived from *t*-butyl acetate and LDA was observed when the amination reaction was quenched at this temperature. This indicates that reaction of oxaziridine **3a** with NaHMDS is faster than with the enolate, and therefore if deprotonation of the ester is reversible, oxaziridine decomposition via reaction with NaHMDS is likely to be a significant problem. The presence of the imino-aldol side product **24** in the amination reaction indicated that imine **9a** must be formed in the reaction and therefore that there is some O-transfer occurring. However, no oxidation of the enolate was observed, so the most likely candidate for oxidation is the NaHMDS, which was indeed shown to produce imine on reaction with oxaziridine as described above.

In view of the potential problems of amide bases, amine-free methods were sought and an obvious candidate was Rathke's anion **26** (lithio *t*-butyl acetate). This could be synthesised according to the literature procedure[17] by deprotonation of *t*-butyl acetate with LDA in hexane, followed by evaporation of the solvent and diisopropylamine.

Reaction between this species and oxaziridine **3a** in dichloromethane (Scheme 13) afforded a 7:10:4 mixture of α-amino ester **19**, aldol **20a** and imino-aldol **24** products (~22% yield of α-amino ester **19**), along with small amounts of amide **23**. Performing the reaction in toluene, tetrahydrofuran, ether or acetonitrile resulted in less clean reactions, with a smaller proportion of α-amino ester **19** observable in the ^{1}H NMR spectra of the crude reaction mixtures. The use of Rathke's anion therefore offered no improvement over the original procedure.

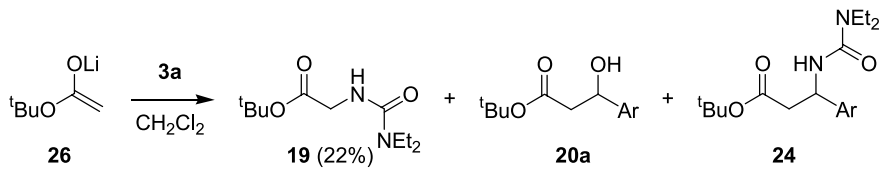
Some of the modified procedures described above were also carried out with the *ortho*-cyano substituted oxaziridine **3b**. Amination of *t*-butyl acetate using NaHMDS as base again afforded no observable aldol product **20b**, but in this case 33% yield of α-amino ester **19** was obtained using only 1 equiv of oxaziridine **3b**. The addition of a second equivalent of oxaziridine had little effect on the reaction, giving 31% yield of α-amino ester **19**. This could be accounted for by a change in the relative reactivity of the oxaziridine with NaHMDS and the enolate: if oxaziridine **3b** reacts with the enolate faster than its reaction with NaHMDS, this would remove the need for 2 equiv of oxaziridine. As stated previously, oxaziridine **3a** reacts with NaHMDS but not the enolate at −78 °C. In contrast, oxaziridine **3b** does react with the enolate derived from *t*-butyl acetate and LDA at −78 °C, as demonstrated by quenching the reaction at this temperature. Therefore, in the amination procedure using NaHMDS as base, at least some of oxaziridine **3b** can react with the enolate rather than NaHMDS at the initial reaction temperature (−78 °C).

Reaction of oxaziridine **3b** with Rathke's anion in dichloromethane gave a slightly improved reaction compared to the *p*-chloro analogue **3a**. The crude product contained an 11:8:5 mixture of α-amino ester **19**, aldol product **20b** and imino-aldol product **24b**, and ~30% yield of α-amino ester **19** was obtained.

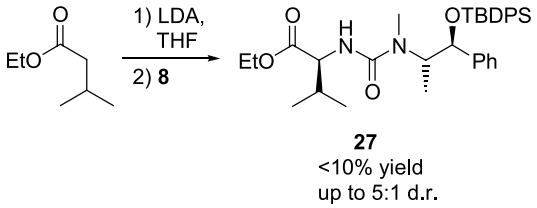
Overall, in spite of some promising results regarding prevention of the aldol reaction by use of NaHMDS, the efficiency of amination of *t*-butyl acetate could not be improved to any significant extent over that initially obtained using LDA. At this stage, it was decided to investigate whether other substrates might be aminated more successfully with these oxaziridines. The initial modification to the substrate simply involved examining amination of a propionate rather than an acetate. However, the reaction of ethyl propionate with oxaziridines **3a** or **3b** using LDA as base gave very low yields of amination (<10%), along with small amounts of tentatively identified imino-aldol and aldol products.

2.4. Attempted asymmetric amination of an ester enolate with 8 and subsequent cleavage of the pseudoephedrine auxiliary

Despite the low yields in amination of ester enolates, we decided to investigate the use of chiral oxaziridine **8**. If this



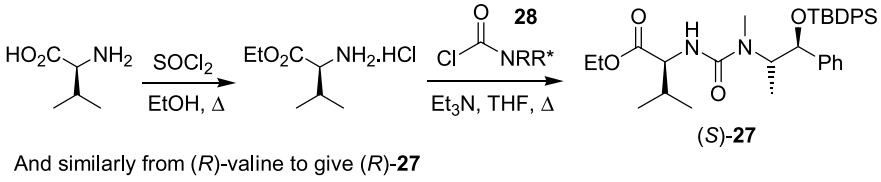
Scheme 13.



Scheme 14.

occurred with high levels of diastereocontrol, this would compensate for the low chemical yields thus far obtained. Ethyl isovalerate was chosen as the test substrate for asymmetric amination as this had given the best stereoselectivity in previous work with the *N*-menthyloxycarbonyl oxaziridine **2**.[7] However, initial reaction of the pseudoephedrine-derived oxaziridine **8** with this substrate was again low yielding (Scheme 14). Partial purification could be achieved by flash chromatography but the products could not be separated from closely running impurities. Comparison of ^{1}H NMR spectra and HPLC traces with those of authentic samples indicated a reasonable degree of selectivity towards formation of (*S*)-amino ester **27** (up to ~5:1), but the impurities prevented accurate quantification of the diastereoselectivity.

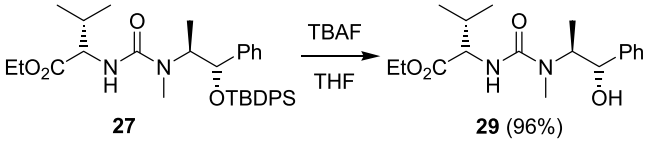
The authentic samples of both diastereomers of the amination product **27** were synthesised in two steps from (*S*)- and (*R*)-valine in 86 and 78% yield, respectively (Scheme 15). The products could be discriminated by HPLC and some analytically useful differences in the ^{1}H NMR spectra (NCH_3 and (C=O)C*H* peaks).



Scheme 15.

The reason for the low yield in this initial amination reaction was unclear, but it was thought that steric interactions between the bulky enolate and oxaziridine could potentially have been the cause. However, amination of the smaller ethyl propionate with pseudoephedrine-derived oxaziridine **8** again proceeded in low yield.

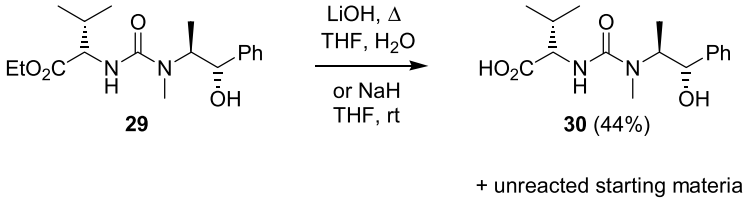
In spite of the poor results obtained on reaction of pseudoephedrine-derived oxaziridine **8** with enolates, study of the auxiliary cleavage in the aminated products **27** was still of interest. It was envisaged that this might be possible via an intramolecular cyclisation of the deprotected alcohol (cf. Scheme 3). The TBDPS protecting group was readily and quantitatively removed to give the free alcohol **29** using tetrabutylammonium fluoride (Scheme 16), but no spontaneous cyclisation was observed under the reaction conditions.



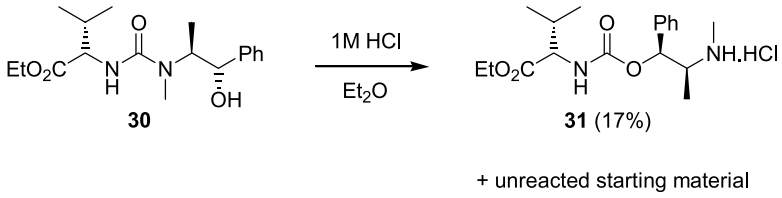
Scheme 16.

Many attempts were made to induce selective intramolecular cleavage of the urea in **29** without success. For instance, basic conditions led to hydrolysis of the amino ester function to afford **30** before any cleavage of the urea was observed (Scheme 17), and the use of Lewis acids ($NiCl_2$ in EtOH; $Ti(O^iPr)_4$ in THF) gave no reaction. Heating **29** in 1 M aqueous hydrochloric acid produced small amounts of the ring-closed oxazolidinone, although the desired amino ester could not be isolated and had presumably been hydrolysed to the amino acid. Interestingly, treatment of **30** with 1 M HCl in diethyl ether afforded small amounts of a rearranged carbamate product **31** along with unreacted starting material (Scheme 18). This structure was confirmed by X-ray crystallography (Fig. 4).

Formation of **31** might suggest that the desired nucleophilic attack of the hydroxyl group on the urea had occurred, but that the 'wrong' nitrogen had subsequently been eliminated. However, a study of the literature[18] revealed that the usual mechanism of urea hydrolysis actually proceeds via an isocyanate intermediate. For the unsymmetrical pseudoephedrine urea **29**, only one isocyanate intermediate can potentially form, as the pseudoephedrine nitrogen does not have the necessary proton for isocyanate formation in that direction (Scheme 19). The isocyanate could then be intercepted by the pseudoephedrine hydroxyl group to give the rearranged product, which precipitates out of the reaction mixture as its hydrochloride salt **31**.



Scheme 17.



Scheme 18.

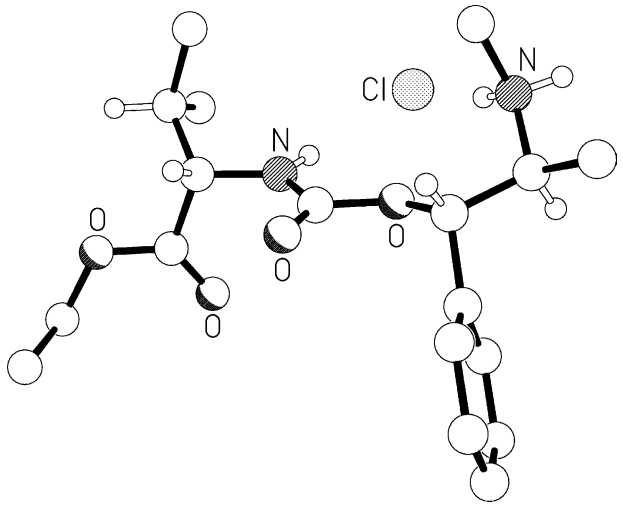


Figure 4. X-ray crystal structure of **31**.

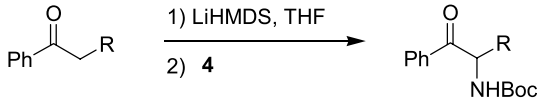
2.5. Amination of more acidic substrates

Because incomplete or reversible deprotonation had been identified as a key issue when using NaHMDS as base with esters, it was proposed that the use of more acidic substrates may improve the amination reaction. *i*-Propyl phenylacetate (pK_a of *t*-butyl phenylacetate in DMSO=23.6[16]) was selected first. Equimolar reaction of this substrate, NaHMDS and oxaziridine **3a** gave only trace amounts of amination product along with side products consistent with reaction of NaHMDS and the oxaziridine (including amide **23** and an imino-aldol product). Complete deprotonation of the substrate would have been expected prior to addition of the oxaziridine and this therefore suggests that the deprotonation may be reversible, with 'internal return' of the originally removed proton by the complexed HMDS occurring on addition of the oxaziridine.[15] The equilibrium is presumably pulled in this direction due to a more rapid reaction of the oxaziridine with NaHMDS than with the enolate.

Ketones are generally more acidic than their corresponding esters and so the amination of propiophenone (pK_a in DMSO=24.4)[16] was examined. However, no amination product could be isolated from the reaction of this substrate with oxaziridine **3a** using either LDA (1 equiv **3a**) or NaHMDS (2 equiv **3a**) as base. However, modest yields of amination product were obtained using the ketomalonate-derived oxaziridine **4** with this substrate class (Table 3).

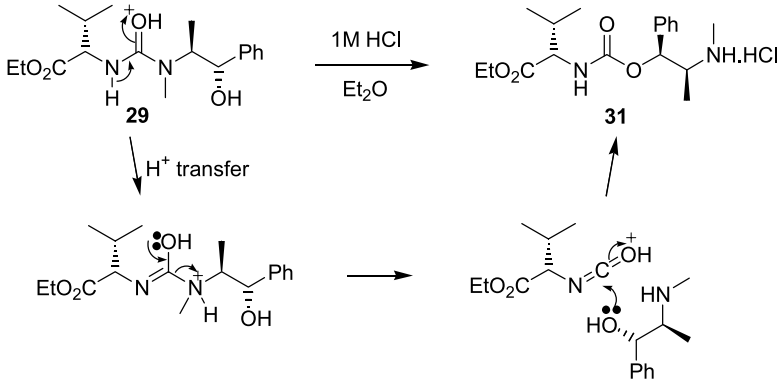
With this substrate class, the opportunity was also taken to examine the use of boron and titanium enolates. The boron enolate was prepared using Bu_2BOTf and DIPEA according to a literature procedure,[19] but gave no amination product on reaction with 1 equiv of oxaziridine **3a**. The titanium enolate, derived using $TiCl_4$ and Bu_3N,[20] again afforded no amination product but instead gave clean conversion to the α-chloro ketone **33** in 84% yield (Scheme 20). The full scope of this procedure was not determined, although deoxybenzoin could also be chlorinated efficiently (86% yield of α-chloro ketone **34**).

Table 3.

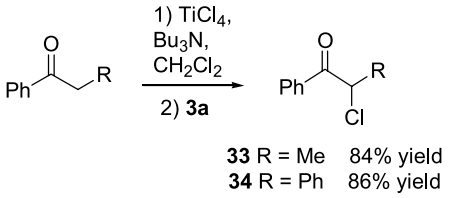


Entry		R	Yield of **32**[a] (%)
1	**a**	H	21
2	**b**	Me	31
3	**c**	Ph	15

[a] Using 1 equiv of LiHMDS, substrate and oxaziridine **4**.



Scheme 19.



Scheme 20.

A similar reaction had recently been reported for α-chlorination of silyl enol ethers, giving comparable yields for the above substrates (Scheme 21).[21] In this procedure the silyl enol ether had been treated with pyridine and $TiCl_2(O^iPr)_2$, followed by *t*-butyl hydroperoxide. It is likely that this reaction and the oxaziridine-mediated α-chlorination would proceed by analogous mechanisms, due to the similarity of the two processes, and two potential mechanisms had been proposed for the literature reaction (Scheme 21). The first involved oxidation of chloride to an electrophilic chlorine species, which then reacted with the silyl enol ether to give the product. The second proposal involved formation of a titanium enolate and reaction with *t*-butylhydroperoxide followed by attack of chloride anion.

An attempt to develop enantioselective chlorination using pseudoephedrine-derived oxaziridine **8** was unsuccessful, affording racemic α-chloro ketone **33** in low yield. Mechanistically this suggests involvement of an electrophilic chlorine species, as some enantioselectivity might be expected if the reaction proceeded via oxidation of the substrate by the oxaziridine.

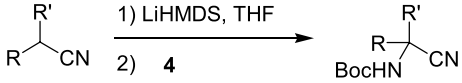
The Page group had achieved most success with their *N*–H oxaziridines when aminating nitrile stabilised carbanions.[4] However, attempted amination of ethyl phenyl cyanoacetate using oxaziridine **3a** and either LiHMDS or NaHMDS as base gave none of the desired product, instead affording ketoacetate **35** and cyano-imine adduct **36** (Scheme 22). These likely originate from oxidation of the enolate as shown, although no mechanistic studies were carried out. The reason for this apparent switch in chemoselectivity from the reaction with *t*-butyl acetate could be a combination of steric and electronic factors. As amination is sensitive to the size of substituents on the oxaziridine ring,[5] it might also be expected to be less favourable when using large nucleophiles such as trisubstituted enolates. In addition, the softer nature of this highly stabilised enolate may also favour the oxidation pathway. Collet had calculated[5] on a model oxaziridine that the nitrogen was almost neutral, whilst the oxygen had a partial negative charge of 0.26 e^-. Electrostatic repulsion between the anionic enolate and oxygen atom might therefore favour the amination pathway, but this effect would be less significant for softer nucleophiles. It is relevant to note that Collet's *N*-alkoxycarbonyl oxaziridines gave exclusive amination with hard enolates, but mixtures of amination and oxidation products on reaction with the softer sulfides, phosphines and amines, and exclusive oxidation on reaction with silyl enol ethers.[5]

In reactions of oxaziridines with sulfides, we have shown that the use of ketone-derived oxaziridines can favour transfer of nitrogen over oxygen.[9] We therefore tested the above nitrile substrate with the 3,3-disubstituted oxaziridine **4**. Pleasingly, this did prove more successful, with moderate yields obtained for range of nitriles with 1 equiv of oxaziridine **4** (Table 4). Additionally, we were able to aminate substituted malonate anions (Table 5), albeit in low yields. Simple unsubstituted malonates (dimethyl- or diethylmalonate) afforded impure products due to competing diamination. However, it is notable that, in contrast to the aminations of the same anions reported by Page using NH-oxaziridines, no hydrolysis/decarboxylation was observed. The use of 1.5 equiv of oxaziridine **4** had mixed results, increasing the yield of α-amino ester in some examples (up to 70% yield, e.g., Table 4, entry 6), but reducing the yield for others.

2.6. Reaction with silyl enol ethers

Given the problems encountered with the base-sensitivity of

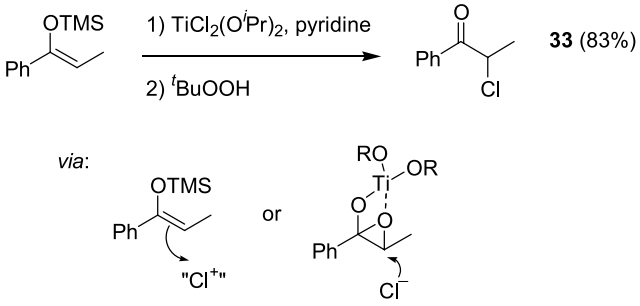
Table 4.



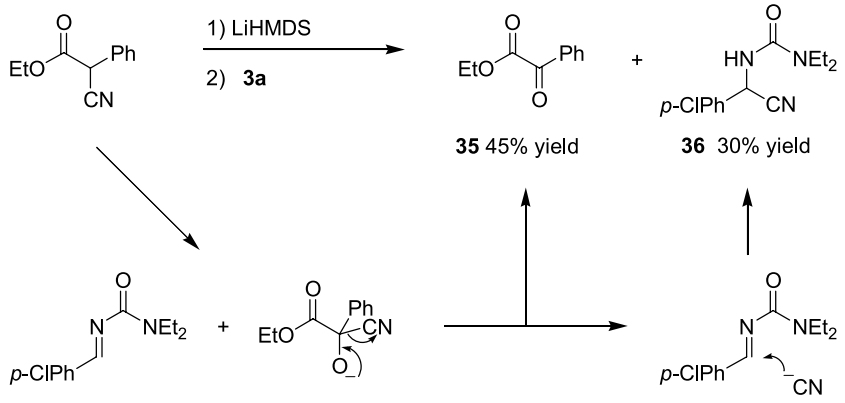
37

Entry		R	R′	Yield of **37**[a] (%)
1	**a**	C_6H_5	H	45
2	**b**	*p*-$MeOC_6H_4$	H	20
3	**c**	*p*-ClC_6H_4	H	46
4	**d**	EtO_2C	H	33
5	**e**	$^tBuO_2C$	H	20
6	**f**	EtO_2C	Ph	50 (70%)[b]

[a] Using 1 equiv of LiHMDS, substrate and oxaziridine **4**.
[b] 1.5 equiv oxaziridine **4** employed.

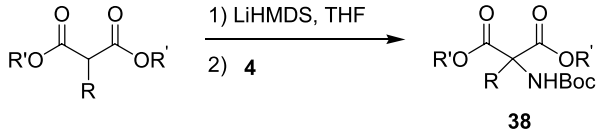


Scheme 21.



Scheme 22.

Table 5.



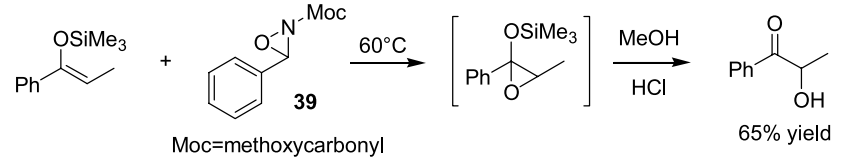
Entry		R	R′	Yield of **38**[a] (%)
1	**a**	Me	Me	30
2	**b**	Me	Et	22

[a] Using 1 equiv of LiHMDS, substrate and oxaziridine **4**.

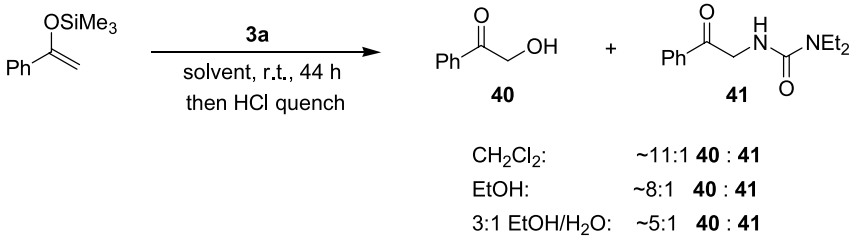
the oxaziridine reagents, the use of neutral reaction conditions with silyl enol ethers as substrates was an attractive possibility. Collet had reported that reaction of the TMS enol ether of propiophenone with *N*-alkoxycarbonyl oxaziridine **39** gave oxidation but no amination of the substrate (Scheme 23, solvent not reported).[5]

When we carried out the similar reaction of acetophenone TMS enol ether with oxaziridine **3a** in dichloromethane, this was also found to be selective for oxidation, but in this case a small amount of amination product **41** could also be detected (~11:1 oxidation to amination, Scheme 24). Study of the reaction between oxaziridines and sulfides had demonstrated that the use of more polar solvents could increase the ratio of amination to oxidation.[22] This same effect was also observed on the reaction of acetophenone TMS enol ether with oxaziridine **3a** (Scheme 24). Thus, performing the reaction in ethanol afforded a ~8:1 mixture of oxidation and amination products, and this ratio could be further improved to ~5:1 by using a 3:1 ethanol/water solvent mixture. Although the amount of amination had been increased, the reaction was still selective for oxidation and in the latter case only ~60% of the oxaziridine reacted, presumably due to competing hydrolysis of the TMS enol ether. Potential origins of the solvent polarity effect have been discussed in the previously reported study of sulfimidation, involving preferential stabilisation by high polarity solvents of the more polar amination transition state compared to that of oxidation.[22]

Examination of other oxaziridines in this reaction was also carried out. Reaction of acetophenone TMS enol ether with ketomalonate-derived oxaziridine **4** or 3-methoxycarbonyl oxaziridine **7** in ethanol gave improved ratios of oxidation–amination products (~1.8:1 and ~2.8:1 **40**:**41**, respectively), but conversion was less clean with substantial amounts of decomposition products also being formed. 3-Methoxycarbonyl 3-phenyl oxaziridine **6** gave very little reaction even after 44 h at room temperature, but that which had occurred was selective for oxidation, and no amination could be detected. These results indicate that there is



Scheme 23.



Scheme 24.

potential for optimisation of the amination pathway by further structural modifications to the oxaziridine, although a considerable improvement is required.

3. Conclusions

We have successfully prepared a structurally diverse range of novel oxaziridines and tested these in the amination of enolates. With aldehyde-derived *N*-carboxamido-oxaziridine **3a**, the use of a sodium base was found to reduce the amount of aldol side-product. For *ortho*-cyanophenyl-oxaziridine **3b**, the aldol side-product was found to be removed from the reaction mixture by washing with acid, probably by intramolecular cyclisation of the aldol hydroxyl group onto the nitrile. While these new reagents and conditions disappointingly did not improve the isolated yield of the amination product, they provide useful ways of facilitating isolation and purification of the amination product. A chiral oxaziridine **8** allowed us to test the concept of a novel 'self-cleaving' amino alcohol protecting group, and appeared to offer promising diastereoselectivity in ester enolate amination, but yields were again low. In a further study with aldehyde-derived oxaziridine **3a**, products derived from deprotonation of the oxaziridine ring were identified, suggesting that ketone-derived oxaziridines may be worthy of investigation. However, ketomalonate-derived oxaziridine **4** afforded significant amination yields only for relatively stabilised carbanions. Despite the lack of success in improving the enolate amination yields, the study has revealed interesting and useful information about the process, and the work has led to development of other methodology that may be of wider value: for example, the $Ti(O^iPr)_4$-mediated synthesis of *N*-carboxamido-imines and the alpha-chlorination of ketones. Moreover, the novel oxaziridines prepared are now available for other processes such as heteroatom transfer to amine and sulfide nucleophiles, which are synthetically useful in themselves.[9]

4. Experimental

4.1. General details

Diethyl ether and tetrahydrofuran were distilled before use from sodium-benzophenone ketyl, and dichloromethane from calcium hydride. Other solvents and reagents were purified according to standard procedures where appropriate. Solutions of butyllithium were titrated against diphenylacetic acid before use. Reaction temperatures were recorded as bath temperatures. Flash chromatography was performed using BDH F_{254} silica gel. Analytical thin layer chromatography was performed on pre-coated Merck silica gel 60 F_{254} glass backed plates and visualised by ultraviolet light and potassium permanganate, anisaldehyde, ceric ammonium nitrate or ninhydrin stains as appropriate. NMR analyses were performed on Bruker 250, 300, 400 or 500 MHz instruments in $CDCl_3$; chemical shifts are quoted in ppm relative to TMS (as referenced to residual $CHCl_3$ $\delta_H=7.26$ or $CDCl_3$ $\delta_C=77.0$ ppm), with coupling constants quoted in Hertz. Infrared analyses were recorded as a thin film (produced from evaporation of a dichloromethane solution) unless otherwise stated, on NaCl plates using a Mattson Satellite FTIR spectrometer from 4000 to 600 cm^{-1}. Mass spectrometry was carried out under CI (ammonia reagent gas) or FAB conditions using a Micromass Autospec-Q spectrometer at the Imperial College Mass Spectrometry Service. Where compounds contain chlorine, the peaks quoted refer to ^{35}Cl-containing isotopes. Elemental analysis was carried out by Mr. Stephen Boyer at the University of North London. Optical rotation measurements were performed on an Optical Activity Polarimeter and the reported $[\alpha]_D$ values are given in 10^{-1}deg cm^2 g^{-1}. X-ray crystal structures were obtained at the Imperial College Crystallography Service.[31]

4.2. Synthesis of oxaziridines

4.2.1. Synthesis of *N*-carboxamido-oxaziridines.

4.2.1.1. General procedures for preparation of *N*-diethylcarboxamido benzaldimines 9. *Method A*. A solution of *N*,*N*-diethylurea (1.0 equiv), aldehyde (1.0 equiv) and $TsOH\cdot H_2O$ (catalyst) in toluene under nitrogen was heated at reflux under Dean–Stark conditions. After the reaction was complete it was cooled to room temperature and evaporated to afford the crude imine **9**.

Method B. To *N*,*N*-diethylurea (1.0 equiv) and aldehyde (1.0 equiv) in THF (4 ml/mmol) under nitrogen was added titanium (IV) isopropoxide (1.2 equiv). After stirring at room temperature until completion of the reaction, water was added and the mixture extracted with ethyl acetate (×2). The combined organics were washed with water (×2), dried over $MgSO_4$, filtered and evaporated to afford the crude imine **9**.

Imine **9a**. *Method A*. *N*,*N*-Diethylurea (3.6 g, 30 mmol), *p*-chlorobenzaldehyde (4.3 g, 30 mmol) and $TsOH\cdot H_2O$ (50 mg) in toluene (60 ml) were allowed to react according to the above procedure for 19 h to afford the crude imine **9a** (7.5 g) as a brown oil with a 9:1 imine–aldehyde ratio by ^1H NMR, δ_H (250 MHz, $CDCl_3$) 8.98 (1H, s, N=CH), 7.83 (2H, d, $J=8.4$ Hz, Ar-H), 7.41 (2H, d, $J=8.4$ Hz, Ar-H), 3.59 (2H, q, $J=7.0$ Hz, NCH_2), 3.47 (2H, q, $J=7.0$ Hz, NCH_2), 1.20 (3H, t, $J=7.0$ Hz, NCH_2CH_3), 1.15 (3H, t, $J=7.0$ Hz, NCH_2CH_3).

Method B. *N*,*N*-Diethylurea (232 mg, 2.0 mmol), *p*-chlorobenzaldehyde (282 mg, 2.0 mmol) and titanium (IV) isopropoxide (0.72 ml, 2.4 mmol) were allowed to react according to the above procedure for 20 h to afford crude imine **71a** (467 mg) as a pale yellow oil with a 10:1 imine–aldehyde ratio.

Imine **9b**. *Method A*. *N*,*N*-Diethylurea (1.5 g, 13 mmol), *o*-cyanobenzaldehyde (1.7 g, 13 mmol) and $TsOH\cdot H_2O$ (50 mg) in toluene (40 ml) were allowed to react according to the above procedure for 5 h to afford the crude imine **9b** (3.0 g) as a dark brown oil, δ_H (250 MHz, $CDCl_3$) 9.27 (1H, s, N=CH), 8.08–7.60 (4H, m, Ar-H), 3.69 (2H, q, $J=7.1$ Hz, NCH_2), 3.52 (2H, q, $J=7.1$ Hz, NCH_2), 1.25 (3H, t, $J=7.1$ Hz, NCH_2CH_3), 1.19 (3H, t, $J=7.1$ Hz, NCH_2CH_3.

4.2.1.2. General procedure for preparation of 2-diethylcarboxamido-3-aryloxaziridines 3. To a solution of the crude imine **9** (1.0 equiv) in CH_2Cl_2 (4 ml/mmol) and

saturated aqueous K_2CO_3 (4 ml/mmol) was added *m*CPBA (70–75%, ~3.0 equiv) in CH_2Cl_2 (4 ml/mmol). The mixture was vigorously stirred until completion of the reaction and worked up by addition of water. This was extracted with CH_2Cl_2 (×2) and the combined organics dried over $MgSO_4$, filtered, evaporated and purified by flash chromatography (5–25% EtOAc in petrol) to afford the oxaziridine **3**.

2-(Diethylcarboxamido)-3-(p-chlorophenyl)oxaziridine **3a**. Crude *p*-chlorobenzaldimine **9a** (7.5 g), prepared by the Dean–Stark method, was reacted according to the above procedure for 5 h to afford the oxaziridine **3a** (4.9 g, 63% from aldehyde) as a low-melting solid, ν_{max} (film)/cm^{-1} 2977, 2935, 2875, 1703 (br), 1601, 1495, 1428, 1382, 1269, 1091, 738; δ_H (250 MHz, $CDCl_3$) 7.43 (2H, d, J=8.9 Hz, Ar-H), 7.40 (2H, d, J=8.9 Hz, Ar-H), 5.18 (1H, s, oxaziridine-H), 3.63 (1H, dq, J=14.3 Hz, 7.1, NCH_AH_B), 3.53 (1H, dq, J=14.3, 7.1 Hz, NCH_AH_B), 3.40 (1H, qd, J=7.1, 3.6 Hz, NCH_AH_B), 3.39 (1H, qd, J=7.1, 3.6 Hz, NCH_AH_B), 1.19 (6H, t, J=7.1 Hz, NCH_2CH_3); δ_C (62.5 MHz, $CDCl_3$) 160.8, 136.7, 131.6, 129.3, 128.9, 77.5, 42.0, 41.9, 14.4, 12.7; MS (EI+) *m*/*z* 254 (M^+). Found: $[M]^+$, 254.0819, $C_{12}H_{15}N_2O_2Cl$ requires 254.0822.

Similar reaction using crude *p*-chlorobenzaldimine **9a** (467 mg) prepared by the titanium isopropoxide method afforded the oxaziridine **3a** (340 mg, 67% from aldehyde).

2-(Diethylcarboxamido)-3-(o-cyanophenyl)oxaziridine **3b**. Crude *o*-cyanobenzaldimine **9b** (3.0 g), prepared by the Dean–Stark method, was reacted according to the above procedure for 3 h to afford the oxaziridine **3b** (0.97 g, 30% from aldehyde) as a pale yellow oil, ν_{max} ($CHCl_3$ solution)/cm^{-1} 2972, 2937, 2361, 2228, 1698, 1601, 1430, 1271; δ_H (250 MHz, $CDCl_3$) 7.68–7.46 (4H, m, Ar-H), 5.52 (1H, s, oxaziridine-H), 3.56 (1H, dq, J=14.4, 7.2 Hz, NCH_AH_B), 3.50 (1H, dq, J=14.4, 7.2 Hz, NCH_AH_B), 3.34 (1H, qd, J=7.0, 1.7 Hz, NCH_AH_B), 3.33 (1H, qd, J=7.0, 1.7 Hz, NCH_AH_B), 1.14 (3H, t, J=7.0 Hz, NCH_2CH_3), 1.12 (3H, t, J=7.2 Hz, NCH_2CH_3); δ_C (67 MHz, $CDCl_3$) 160.0 (C), 136.4 (C), 133.2 (CH), 133.1 (CH), 130.7 (CH), 128.4 (CH), 116.3 (C), 112.7 (C), 74.8 (CH), 42.1 (CH_2), 42.0 (CH_2), 14.4 (CH_3), 12.6 (CH_3); MS (EI+) *m*/*z* 245 (M^+, 3.48%). Found: $[M]^+$, 245.1174, $C_{13}H_{15}N_3O_2$ requires 245.1164. Found: C, 63.46; H, 6.23; N, 16.99. $C_{13}H_{15}N_3O_2$ requires C, 63.66; H, 6.16; N, 17.13%.

2-(Diethylcarboxamido)-3-phenyl-3-(trifluoromethyl)oxaziridine **5**. To *N*,*N*-diethylurea (232 mg, 2.0 mmol) and trifluoroacetophenone (280 µl, 2.0 mmol) in THF (4 ml) under nitrogen was added titanium (IV) isopropoxide (720 µl, 2.4 mmol). After stirring at reflux for 6 h, water (20 ml) was added and the mixture extracted with ethyl acetate (2×20 ml). The combined organics were washed with water (2×20 ml), dried over $MgSO_4$, filtered and evaporated to afford the crude imine **10** as a yellow oil. To a solution of the crude imine **10** in CH_2Cl_2 (10 ml) and saturated aqueous K_2CO_3 (10 ml) was added *m*CPBA (50–55%, 2.0 g, ~6.0 mmol) in CH_2Cl_2 (10 ml). After stirring at room temperature for 5 h, water (40 ml) was added and the mixture extracted with CH_2Cl_2 (2×40 ml). The combined organics were dried over $MgSO_4$, filtered, evaporated and purified by flash chromatography (5–10% EtOAc in petrol) to afford the oxaziridine **5** (107 mg, 19% from ketone) as a white crystalline solid, mp 95–96 °C; ν_{max}/cm^{-1} 3414, 2981, 1720, 1428, 1333, 1268, 1205, 1166, 957, 725, 697; δ_H (250 MHz, $CDCl_3$) 7.65–7.35 (5H, m, Ar-H), 3.58 (1H, dq, J=14.4, 7.2 Hz, NCH_AH_B), 3.31 (1H, dq, J=14.1, 7.1 Hz, NCH_AH_B), 3.18 (1H, dq, J=14.4, 7.2 Hz, NCH_AH_B), 2.84 (1H, dq, J=14.1, 7.1 Hz, NCH_AH_B), 1.23 (3H, t, J=7.2 Hz, NCH_2CH_3), 0.62 (3H, t, J=7.1 Hz, NCH_2CH_3); δ_C (62.9 MHz, $CDCl_3$) 155.9 (C), 131.2 (CH), 128.4 (CH), 127.9 (CH), 124.8 (C), 121.2 (CF_3, q, J=280 Hz), 80.6 (C_{ring}, q, J=39 Hz), 41.3 (CH_2), 41.2 (CH_2), 13.5 (CH_3), 12.0 (CH_3); δ_F (235 MHz, $CDCl_3$) −79.5 (CF_3); *m*/*z* (CI, NH_3) 306 ($[M+NH_4]^+$, 43%), 289 ($[M+H]^+$, 11). Found: $[M+NH_4]^+$, 306.1426. $C_{13}H_{19}N_3O_2F_3$ requires 306.1429. Structure confirmed by X-ray crystallography (recrystallisation from EtOAc/petrol).[31]

4.2.1.3. Synthesis of (1*S*,2*S*)-(+)-pseudoephedrine-derived oxaziridine 8. *O-TBDPS-N-chlorocarbonyl-(1S,2S)-pseudoephedrine* **11**. To a solution of (1*S*,2*S*)-(+)-pseudoephedrine hydrochloride (4.0 g, 20 mmol) in CH_2Cl_2 (40 ml) under nitrogen was added TBDPSCl (5.45 ml, 21 mmol) and triethylamine (5.85 ml, 42 mmol). After stirring at room temperature for 24 h diethyl ether (8 ml) was added and after 10 min the mixture was filtered. The filtrate was evaporated to afford the crude *O*-TBDPS pseudoephedrine (9.88 g) as a white oily solid, δ_H (250 MHz, $CDCl_3$) 7.74–7.12 (15H, m, Ar-H), 4.61 (1H, d, J=6.7 Hz, PhCH), 2.83 (1H, dq, J=6.7, 6.4 Hz, NCH), 2.25 (3H, s, NCH_3), 1.02 (9H, s, $C(CH_3)_3$), 0.78 (3H, d, J=6.4 Hz, $NCHCH_3$).

To a solution of the crude *O*-TBDPS pseudoephedrine (8.09 g, 16.4 mmol, assuming 100% yield) in THF (50 ml) under nitrogen was added triethylamine (3.2 ml, 22.9 mmol) and 4-dimethylaminopyridine (50 mg). After cooling to 0 °C, triphosgene (1.94 g, 6.55 mmol) was added in one portion. After stirring for 30 min at 0 °C and 10 min at room temperature, water (100 ml) was cautiously added and the solution extracted into ethyl acetate (3×50 ml). The combined organics were washed with brine (50 ml), dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give the crude title compound **11** as a pale yellow viscous oil (8.48 g). This was of sufficient purity for further reaction but could be purified by flash chromatography (5% EtOAc in petrol) to provide an analytically pure sample as a colourless oil, $[\alpha]_D^{19}$ +78.5 (*c* 0.93, $CHCl_3$); ν_{max}/cm^{-1} 3071, 2933, 1738, 1427, 1293, 1242, 1106, 823, 703, 612, 504; δ_H (300 MHz, $CDCl_3$, 2 rotamers a and b in 9:5 ratio) 7.71–7.18 (15H, m, Ar-H), 4.76–4.50 (2H, m, NCH and PhCH), 2.63 (3H, s, NCH_3 a), 2.54 (3H, s, NCH_3 b), 1.03 (9H, s, $C(CH_3)_3$ b), 1.01 (9H, s, $C(CH_3)_3$ a), 0.91 (3H, d, J=6.9 Hz, $NCHCH_3$ b), 0.86 (3H, d, J=6.8 Hz, $NCHCH_3$ a); δ_C (75.4 MHz, $CDCl_3$, 2 rotamers with some superposition of peaks) 150.3 (C), 150.0 (C), 140.8 (C), 140.5 (C), 136.1 (CH), 136.0 (CH), 134.8 (CH), 133.4 (C), 132.9 (C), 132.8 (CH), 129.7 (CH), 129.6 (CH), 129.5 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.6 (CH), 127.5 (CH), 76.4 (CH), 61.2 (CH), 59.9 (CH), 33.2 (CH_3), 31.0 (CH_3), 26.9 (CH_3), 19.2 (C), 14.3 (CH_3), 14.2 (CH_3); *m*/*z* (CI, NH_3) 483 ([M+

$NH_4]^+$, 87%), 466 ($[M+H]^+$, 20). Found: $[M+NH_4]^+$, 483.2231. $C_{27}H_{36}N_2O_2SiCl$ requires 483.2235.

O-TBDPS-N-carboxamido-(1S,2S)-pseudoephedrine **12**. To a solution of the crude carbamoyl chloride **11** (1.81 g, 3.5 mmol, assuming 100% yield) in diethyl ether (30 ml) was added ~35% aqueous ammonia solution (40 ml). The ammonia solution was replenished periodically until the reaction was complete as evidenced by thin layer chromatography. The mixture was separated and the aqueous layer re-extracted with diethyl ether (2×30 ml). The combined organics were washed with brine (30 ml), dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. Flash chromatography (20–100% EtOAc in petrol) afforded the title compound **12** (1.47 g, 94% from pseudoephedrine hydrochloride) as a colourless viscous glass, $[\alpha]_D^{19}$ +67.9 (*c* 1.12, $CHCl_3$); ν_{max}/cm^{-1} 3347, 3204, 2931, 2235, 1659, 1599, 1488, 1404, 1107, 910, 823, 703, 611, 504; δ_H (250 MHz, $CDCl_3$) 7.68–7.14 (15H, m, Ar-H), 4.72 (2H, br s, NH_2), 4.55 (1H, d, J=7.6 Hz, PhCH), 4.30 (1H, br m, NCH), 2.36 (3H, br s, NCH_3), 0.98 (9H, s, $C(CH_3)_3$), 0.82 (3H, d, J=6.8 Hz, NCHCH_3); δ_C (75.4 MHz, $CDCl_3$, 1 aromatic CH not found) 159.6 (C), 141.1 (C), 135.8 (CH), 135.8 (CH), 133.4 (C), 132.7 (C), 129.5 (CH), 129.3 (CH), 127.8 (CH), 127.4 (CH), 127.2 (CH), 127.1 (CH), 77.0 (CH), 56.7 (CH), 28.4 (CH_3), 26.8 (CH_3), 19.0 (C), 14.1 (CH_3); *m/z* (CI, NH_3) 447 ($[M+H]^+$, 100%). Found: $[M+H]^+$, 447.2466. $C_{27}H_{35}N_2O_2Si$ requires 447.2468.

2-(N-Methyl-N-((1′S,2′S)-1′-TBDPSO-1′-phenyl-2′-propyl) carboxamido)-3-(p-chlorophenyl)oxaziridine **8**. To a solution of the urea **12** (915 mg, 2.05 mmol) and *p*-chlorobenzaldehyde (290 mg, 2.05 mmol) in THF (10 ml) was added titanium (IV) isopropoxide (750 μl, 2.46 mmol). After stirring at room temperature under nitrogen for 16 h, water (40 ml) was added and the mixture extracted with ethyl acetate (2×60 ml). The combined organics were washed with water (2×40 ml), dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to afford the crude imine **13** (1.1 g) as a colourless viscous oil with a 8:1 imine–aldehyde ratio, δ_H (250 MHz, $CDCl_3$, 2 rotamers a and b in 2:5 ratio) 8.83 (1H, s, N=CH a), 8.52 (1H, s, N=CH b), 7.84–7.00 (19H, m, Ar-H), 5.00–4.80 (1H, br m, NCH), 4.70 (1H, d, J=8.3 Hz, PhCH a), 4.62 (1H, d, J=5.4 Hz, PhCH b), 2.88 (3H, s, NCH_3 b), 2.72 (3H, s, NCH_3 a), 1.05 (3H, d, J=7.0 Hz, NCHCH_3 b), 0.96 (9H, s, $C(CH_3)_3$ b), 0.94 (9H, s, $C(CH_3)_3$ a), 0.89 (3H, d, J=7.0 Hz, NCHCH_3 a).

To a solution of the crude imine **13** (1.1 g, 2.05 mmol, assuming 100% yield) in CH_2Cl_2 (15 ml) and saturated aqueous K_2CO_3 (12 ml) was added *m*CPBA (70–75%, 1.5 g, ~6.0 mmol) in CH_2Cl_2 (10 ml). After stirring at room temperature for 5 h, water (60 ml) was added and the mixture extracted with CH_2Cl_2 (2×30 ml). The combined organics were dried over $MgSO_4$, filtered, evaporated and purified by flash chromatography (3–7% EtOAc in petrol) to afford the oxaziridine **8** (700 mg, 58% from urea **12**) as a white foam, $[\alpha]_D^{22}$ −4.2 (*c* 2.16, $CHCl_3$); ν_{max}/cm^{-1} 3071, 2932, 2858, 2248, 1692, 1602, 1427, 1242, 1090, 824, 702; δ_H (300 MHz, $CDCl_3$, 2 rotamers a and b in ~1:2 ratio) 7.71–6.82 (19H, m, Ar-H), 5.06 (1H, s, oxaziridine-H a), 5.03 (1H, s, oxaziridine-H b), 5.06–4.90 (1H, m, NCH b), 4.72–4.64 (2H, m, PhCH a and NCH a), 4.48 (1H, d, J=7.3 Hz, PhCH b), 2.85 (3H, s, NCH_3 b), 2.72 (3H, s, NCH_3 a), 1.00 (9H, s, $C(CH_3)_3$ a), 0.98–0.92 (12H, m, $C(CH_3)_3$ b and NCHCH_3 b), 0.89 (3H, d, J=6.6 Hz, NCHCH_3 a); δ_C (75.4 MHz, $CDCl_3$, 2 rotamers with some superposition of peaks) 161.7 (C), 161.6 (C), 141.0 (C), 140.7 (C), 136.1 (CH), 136.0 (CH), 133.6 (C), 133.1 (C), 132.8 (C), 131.8 (C), 131.6 (C), 130.8 (C), 129.8 (CH), 129.5 (CH), 129.3 (CH), 128.8 (CH), 128.7 (CH), 128.0 (CH), 127.8 (CH), 127.5 (CH), 127.3 (CH), 127.2 (CH), 127.1 (CH), 77.7 (CH), 77.1 (CH), 76.8 (CH), 76.3 (CH), 57.6 (CH), 57.3 (CH), 29.3 (CH_3), 27.0 (CH_3), 26.9 (CH_3), 19.3 (C), 19.2 (C), 15.1 (CH_3), 14.1 (CH_3), 13.6 (CH_3); *m/z* (FAB) 585 ($[M+H]^+$, 0.6%). Found: C, 70.0; H, 6.28; N, 4.74. $C_{34}H_{37}N_2O_3SiCl$ requires C, 69.8; H, 6.37; N, 4.79%.

4.2.2. Synthesis of *N*-Boc oxaziridines. *N*-Boc oxaziridines **1**[5] and **4**[9] were prepared according to literature procedures.

N-Boc -3-Methoxycarbonyloxaziridine **7**. A mixture of methyl *N*-Boc glycinate **14** (0.9 ml, 6.0 mmol) and NBS (1.08 g, 6.0 mmol) in CCl_4 (12 ml) under nitrogen was irradiated with a 500 W bulb (distance ~10 cm) for 1 h (temperature of solution kept below 30 °C using a water bath). The reaction was filtered and evaporated to afford the crude bromide **15** as a yellow oil, δ_H (250 MHz, $CDCl_3$) 6.35 (1H, br d, J=10.6 Hz, CH), 6.00 (1H, br d, J=10.6 Hz, NH), 3.85 (3H, s, CH_3), 1.47 (9H, s, $C(CH_3)_3$). To the crude bromide **15** in THF (6 ml) at −78 °C under nitrogen was added triethylamine (0.70 ml, 5.0 mmol) and the reaction stirred for 30 min at −78 °C to afford a crude imine solution **16**.Meanwhile, to a solution of purified *m*CPBA (0.43 M in CH_2Cl_2, 12.7 ml, 5.5 mmol) at −78 °C under nitrogen was slowly added *n*-BuLi (2.5 M in hexanes, 2.1 ml, 5.3 mmol) and the reaction stirred for 30 min. The cold crude imine solution **16** was then quickly filtered under nitrogen into the *m*CPBA solution. After stirring for 2 h at −78 °C, the reaction was allowed to warm to −50 °C then quenched with saturated aqueous sodium bicarbonate solution (20 ml). The layers were separated and the aqueous layer re-extracted with CH_2Cl_2 (2×20 ml). The combined organics were dried over $MgSO_4$, filtered, evaporated and purified by flash chromatography (10–20% EtOAc in petrol, then recolumned using 100% CH_2Cl_2) to afford oxaziridine **7** (36 mg, 4%) as a colourless oil, ν_{max}/cm^{-1} 2982, 1773, 1752, 1444, 1373, 1251, 1152, 1019, 846; δ_H (250 MHz, $CDCl_3$, mixture of cis and trans isomers in a ratio of 31:69) 4.64 (1H, s, oxaziridine-H cis), 4.63 (1H, s, oxaziridine-H trans), 3.86 (3H, s, CH_3), 1.51 (9H, s, $C(CH_3)_3$); δ_C (101 MHz, $CDCl_3$, cis and trans isomers) 164.6 (C), 164.5 (C), 158.8 (C), 157.5 (C), 86.5 (C), 85.8 (C), 71.3 (CH), 71.2 (CH), 53.4 (2×CH_3), 27.7 (CH_3), 27.6 (CH_3); *m/z* (CI, NH_3) 221 ($[M+NH_4]^+$, 44%). Found: $[M+NH_4]^+$, 221.1131.$C_8H_{17}N_2O_5$ requires 221.1137.

4.2.2.1. Synthesis of methyl phenylglycinate-derived oxaziridine 6. *Methyl (R)-N-Boc-phenylglycinate* **17**.[23] To a suspension of methyl phenylglycinate hydrochloride (1.0 g, 5 mmol) in THF (40 ml) at 0 °C under nitrogen was added triethylamine (0.73 ml, 5.2 mmol). After stirring at room temperature for 15 min, Boc anhydride (1.64 g, 7.5 mmol) was added. After a further 2 h the reaction was filtered, evaporated and purified by flash chromatography

(15% EtOAc in petrol) to afford *N*-Boc phenylglycine methyl ester **17** (1.3 g, 98%) as a white solid, δ_H (250 MHz, $CDCl_3$) 7.38–7.32 (5H, m, Ar-H), 5.53 (1H, br, NH), 5.32 (1H, br d, $J=7.3$ Hz, CH), 3.72 (3H, s, CH_3), 1.43 (9H, s, $C(CH_3)_3$). Consistent with literature.[23]

Methyl N-Boc-α-iminophenylacetate **18**. A mixture of methyl (*R*)-*N*-Boc-phenylglycinate 17 (1.12 g, 4.2 mmol) and NBS (0.98 g, 5.5 mmol) in CCl_4 (12 ml) under nitrogen was irradiated with a 500 W bulb (distance ~10 cm) for 2 h (temperature of solution kept below 30 °C using a water bath). The reaction was filtered and evaporated to afford a ~5:3 mixture of imine **18**: starting material **17**. Flash chromatography (50–80% CH_2Cl_2 in petrol) afforded the imine 18 (0.70 g, 63%) as a colourless oil, ν_{max}/cm^{-1} 2981, 1744, 1719, 1632, 1249, 1217, 1153, 1020; δ_H (250 MHz, $CDCl_3$) 7.76 (2H, br d, $J=7.3$ Hz, Ar-H), 7.47–7.27 (3H, m, Ar-H), 3.81 (3H, s, CH_3), 1.45 (9H, s, $C(CH_3)_3$); δ_C (62.9 MHz, $CDCl_3$) 164.8 (C), 162.4 (C), 160.4 (C), 132.8 (CH), 132.2 (C), 129.0 (CH), 128.6 (CH), 83.0 (C), 52.7 (CH_3), 27.9 (CH_3); *m/z* (CI, NH_3) 264 ($[M+H]^+$, 63%). Found: $[M+H]^+$, 264.1233.$C_{14}H_{18}NO_4$ requires 264.1236.

N-Boc-3-methoxycarbonyl-3-phenyloxaziridine **6**. To a solution of the imine 18 (607 mg, 2.3 mmol) in CH_2Cl_2 (20 ml) and saturated aqueous K_2CO_3 (20 ml) was added *m*CPBA (50–55%, 2.4 g, ~6.9 mmol) in CH_2Cl_2 (20 ml). After stirring at room temperature for 2 h, water (80 ml) was added and the mixture extracted with CH_2Cl_2 (2×60 ml). The combined organics were dried over $MgSO_4$, filtered, evaporated and purified by flash chromatography (50–60% CH_2Cl_2 in petrol) to afford the oxaziridine **6** (584 mg, 91%) as a colourless oil, ν_{max}/cm^{-1} 3065, 2982, 1769, 1763, 1453, 1372, 1246, 1150, 1015, 852, 697; δ_H (250 MHz, $CDCl_3$, mixture of cis and trans isomers in a ratio of 29:71) 7.55–7.23 (5H, m, Ar-H), 3.73 (3H, s, CH_3 cis), 3.70 (3H, s, CH_3 trans), 1.41 (9H, s, $C(CH_3)_3$ cis), 0.97 (9H, s, $C(CH_3)_3$ trans); δ_C (62.9 MHz, $CDCl_3$, cis and trans isomers with some signals superimposed, 1 aromatic CH not found) 164.8 (C), 164.4 (C), 157.4 (C), 156.1 (C), 130.6 (CH), 130.3 (CH), 128.1 (CH), 127.9 (CH), 127.5 (C), 127.4 (CH), 126.9 (CH), 85.2 (C), 84.8 (C), 80.9 (C), 80.6 (C), 52.9 (2×CH_3), 27.1 (CH_3), 26.6 (CH_3); *m/z* (CI, NH_3) 297 ($[M+NH_4]^+$, 100%). Found: $[M+NH_4]^+$, 297.1439.$C_{14}H_{21}N_2O_5$ requires 297.1450.

4.3. Reactions with enolates

4.3.1. Amination using racemic aldehyde-derived oxaziridines 3.

4.3.1.1. Typical procedure: reaction of *t*-butyl acetate with oxaziridine 3a using LDA as base (Table 2, entry 1). To a solution of diisopropylamine (52 µl, 0.37 mmol) in THF (0.5 ml) at 0 °C under nitrogen was added *n*-BuLi (2.38 M in hexanes, 156 µl, 0.37 mmol). After stirring for 30 min the reaction was cooled to −78 °C and *t*-butyl acetate (50 µl, 0.37 mmol) in THF (0.75 ml) added dropwise. After a further 1 h at −78 °C, oxaziridine **3a** (94 mg, 0.37 mmol) in THF (0.75 ml) was added and the reaction allowed to slowly warm to room temperature over 3 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (6 ml) and extracted with CH_2Cl_2 (3×8 ml). The combined organics were dried over $MgSO_4$, filtered and evaporated to afford a crude mixture of amino ester **19** and aldol product **20a** (~4:3 according to ^1H NMR analysis), plus other side products including diethyl urea and amide **23**. Flash chromatography (10–30% EtOAc in petrol) afforded *t*-butyl *N*-(diethylcarboxamido)glycinate **19** (20 mg, 24%) as white needles.

t-Butyl N-(diethylcarboxamido)glycinate **19**. Mp 143–145 °C; ν_{max} ($CHCl_3$ solution)/cm^{-1} 3168, 2927, 2855, 1721, 1614, 1467, 1452, 1215, 1075; δ_H (250 MHz, $CDCl_3$) 4.88–4.78 (1H, br m, NH), 3.93 (2H, d, $J=4.9$ Hz, $NHCH_2$), 3.28 (4H, q, $J=7.2$ Hz, NCH_2CH_3), 1.46 (9H, s, $C(CH_3)_3$), 1.15 (6H, t, $J=7.2$ Hz, NCH_2CH_3); δ_C (67 MHz, $CDCl_3$) 170.5 (C), 156.8 (C), 81.7 (C), 43.2 (CH_2), 41.2 (2×CH_2), 27.9 (3×CH_3), 13.7 (2×CH_3); MS (EI+) *m/z* 231 (M^+H, 20.5%), 175 (M−*t*Bu, 60.4%). Found: $[M+H]^+$, 231.1712. $C_{11}H_{23}N_2O_3$ requires 231.1708.

t-Butyl 3-(p-chlorophenyl)-3-hydroxypropionate **20a**.[24] Isolated as a colourless oil, δ_H (250 MHz, $CDCl_3$) 7.30 (4H, s, Ar-H), 5.04 (1H, dd, $J=7.0$, 5.8 Hz, CH), 3.60 (1H, br s, OH), 2.62–2.60 (2H, m, CH_2), 1.44 (9H, s, $C(CH_3)_3$); *m/z* (CI, NH_3) 274 ($M+NH_4]^+$, 11%), 257 ($[M+H]^+$, 17). Consistent with literature.[24]

Similar reactions with other bases and conditions afforded **19** and **20a** in the yields indicated in Table 2.

4.3.1.2. Reaction of *t*-butyl acetate with oxaziridine 3b using LDA as base. Similar reaction of *t*-butyl acetate (91 µl, 0.67 mmol), oxaziridine **3b** (165 mg, 0.67 mmol) and LDA (prepared from diisopropylamine (103 µl, 0.73 mmol) and *n*-BuLi (2.4 M in hexanes, 290 µl, 0.70 mmol)) using $NaHCO_3/CH_2Cl_2$ work-up gave a mix of amino ester **19** and aldol product **20b** (~1:1). Flash chromatography (10–30% EtOAc in petrol) afforded amino ester **19** (51 mg, 33%) and aldol **20b** (38 mg, 23%).

t-Butyl 3-(o-cyanophenyl)-3-hydroxypropionate **20b**. Isolated as a colourless oil, ν_{max}/cm^{-1}: 3294, 2979, 2932, 2361, 2331, 2224, 1767, 1726, 1686, 1469, 1368; δ_H (250 MHz, $CDCl_3$): 7.30 (1H, d, $J=7.2$ Hz, ArH), 7.53–7.39 (2H, m, ArH), 7.33 (1H, d, $J=7.2$ Hz, ArH), 5.76 (1H, d, $J=6.0$ Hz, C*H*OH), 2.74–2.71 (2H, m, CH_2CO_2t-Bu), 1.39 (9H, s, *t*-Bu); δ_C (62.5 MHz, $CDCl_3$):168.7, 167.4, 146.2, 132.1, 129.3, 129.0, 123.9, 121.6, 81.5, 79.2, 41.2, 27.9; *m/z* (EI) 247 (M^+5%). Found M^+, 247.1207 $C_{14}H_{17}NO_3$ requires: M, 247.1208.

The same procedure using water as the quench, followed by extraction with CH_2Cl_2 (×3) and sequential washing with saturated aqueous $NaHCO_3$, 1 M HCl and brine removed almost all the aldol product **20b**. This could be recovered by basifying the acid wash to pH ~8 with $NaHCO_3$ followed by extraction with CH_2Cl_2.

4.3.1.3. Reaction of oxaziridine 3a with NaHMDS. To NaHMDS (1.04 M in THF, 183 µl, 0.19 mmol) in THF (1 ml) at −78 °C under nitrogen was added oxaziridine **3a** (97 mg, 0.38 mmol) and the reaction allowed to warm to room temperature over 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 ml), extracted with CH_2Cl_2 (3×7 ml) and the organics dried over $MgSO_4$ and evaporated to afford a complex mixture of products

including amide **23**, imine **9a**, aldehyde and diaminal **25**. Flash chromatography (0–30% EtOAc in cyclohexane) afforded the amide **23** (28 mg, 29% based on oxaziridine).

N-(Diethylcarboxamido)-p-chlorobenzamide **23**. Isolated as a colourless oil, ν_{max}/cm^{-1} 3429, 2976, 1692, 1656, 1478, 1260, 1091, 1014, 755; δ_H (250 MHz, $CDCl_3$) 8.64 (1H, br s, NH), 7.79 (2H, d, $J=8.4$ Hz, Ar-H), 7.41 (2H, d, $J=8.4$ Hz, Ar-H), 3.40 (4H, q, $J=7.1$ Hz, NCH_2CH_3), 1.21 (6H, t, $J=7.1$ Hz, NCH_2CH_3); δ_C (62.9 MHz, $CDCl_3$) 166.3 (br C), 153.7 (br C), 138.8 (C), 131.7 (C), 129.4 (CH), 128.8 (CH), 42.2 (br CH_2), 13.3 (br CH_3); *m/z* (LC–MS, ES+) 255 ($[M+H]^+$, 100%). Found: $[M+H]^+$, 255.0898. $C_{12}H_{16}N_2O_2Cl$ requires 255.0900.

Aminal **25**. Not isolated cleanly-tentatively assigned based on the following data: δ_H (400 MHz, $CDCl_3$) 7.37 (2H, d, $J=8.5$ Hz, Ar-H), 7.27 (2H, d, $J=8.5$ Hz, Ar-H), 6.40 (2H, d, $J=7.9$ Hz, NH), 6.18 (1H, t, $J=7.9$ Hz, CH), 3.31 (4H, dq, $J=14.4$, 7.2 Hz, $NCH_AH_BCH_3$), 3.24 (4H, dq, $J=14.4$, 7.2 Hz, $NCH_AH_BCH_3$), 1.26 (12H, t, $J=7.2$ Hz, NCH_2CH_3); *m/z* (LC–MS, ES+) 355 ($[M+H]^+$, 100%), 239 (40).

4.3.1.4. Iminoaldol products 24a and 24b. These were not isolated in pure form, but were tentatively identified as by-products in the reaction between *tert*-butyl acetate/NaHMDS and oxaziridines **3a** and **3b**, respectively, from the following data:

Compound **24a**. δ_H (250 MHz, $CDCl_3$) 7.30–7.22 (4H, m, Ar-H), 5.82 (1H, br d, $J=7.8$ Hz, NH), 5.25 (1H, dt, $J=7.8$, 5.5 Hz, CH), 3.29 (4H, q, $J=7.2$ Hz, NCH_2CH_3), 2.74 (2H, d, $J=5.5$ Hz, CH_2), 1.34 (9H, s, $C(CH_3)_3$), 1.16 (6H, t, $J=7.2$ Hz, NCH_2CH_3); *m/z* (CI, NH_3) 355 ($[M+H]^+$, 100%), 299 (37). Found: $[M+H]^+$, 355.1791. $C_{18}H_{28}N_2O_3Cl$ requires: 355.1788.

Compound **24b**. δ_H (250 MHz, $CDCl_3$) 7.65–7.28 (4H, m, Ar-H), 6.01 (1H, d, $J=6.3$ Hz, NH), 5.44 (1H, apparent q, $J=6.4$ Hz, CH), 3.28 (4H, q, $J=7.2$ Hz, NCH_2CH_3), 2.85 (1H, dd, $J=15.0$, 6.7 Hz, CH_AH_B), 2.80 (1H, dd, $J=15.0$, 6.0 Hz, CH_AH_B), 1.33 (9H, s, $C(CH_3)_3$), 1.15 (6H, t, $J=7.2$ Hz, NCH_2CH_3); *m/z* (CI, NH_3) 346 ($[M+H]^+$, 100%), 290 (51). Found: $[M+H]^+$, 346.2141. $C_{19}H_{28}N_3O_3$ requires 346.2131.

4.3.1.5. Reaction of Rathke's anion 26 with 2-(diethylcarboxamido)-3-(*p*-chlorophenyl)oxaziridine 3a. Similar reaction of Rathke's anion **28** (60 mg, 0.49 mmol) and oxaziridine **3a** (125 mg, 0.49 mmol) in CH_2Cl_2 (3 ml) gave a crude mixture of amino ester **19**, aldol **20a** and imino-aldol **24** (~7:10:4), plus other side products including diethylurea and amide **23**. Flash chromatography (10–30% EtOAc in petrol) afforded semi-purified amino ester **19** (~10:3:1 with amide **23** and imino-aldol product **24**, 37 mg, ~22%).

4.3.2. Asymmetric amination using enantiopure oxaziridine 8.

4.3.2.1. Amination of ethyl isovalerate with oxaziridine 8. To a solution of diisopropylamine (55 µl, 0.39 mmol) in THF (0.5 ml) at 0 °C under nitrogen was added *n*-BuLi (2.5 M in hexanes, 150 µl, 0.37 mmol). After stirring for 30 min the reaction was cooled to −78 °C and ethyl isovalerate (52 µl, 0.35 mmol) in THF (0.5 ml) added dropwise. After a further 1 h at −78 °C, oxaziridine **8** (94 mg, 0.37 mmol) in THF (0.5 ml) was added. After stirring for 4 h at −78 °C, the reaction was allowed to slowly warm to room temperature over 2 h, quenched with saturated aqueous $NaHCO_3$ (5 ml) and extracted with CH_2Cl_2 (3×8 ml). The combined organics were dried over $MgSO_4$, filtered and evaporated to afford a complex mixture of products. The aminated product **27** could not be separated from co-running impurities by flash chromatography (5–15% EtOAc in petrol), but comparison of ^1H NMR and HPLC traces with authentic samples, after partial purification, indicated some selectivity towards formation of the (*S*)-stereocentre (dr ~5:1).

4.3.2.2. Synthesis of authentic diastereomeric amination products. *Ethyl N-(N-methyl-N-((1′S,2′S)-1′-TBDPSO-1′-phenyl-2′-propyl)carboxamido)-(S)-valinate* (()-**27**). To a suspension of (*S*)-(+)-valine (585 mg, 5.0 mmol) in ethanol (5 ml) at −5 °C under nitrogen was added dropwise thionyl chloride (0.95 ml, 13.0 mmol). After heating to reflux for 4 h the reaction was allowed to cool and evaporated to afford (*S*)-(+)-valine ethyl ester hydrochloride (878 mg, 97%) as an off-white solid, δ_H (250 MHz, DMSO-d_6) 8.41 (2H, br s, NH_2), 4.32–4.11 (2H, m, CH_3CH_2O), 3.86 (1H, d, $J=4.8$ Hz, NCH), 2.16 (1H, m, $(CH_3)_2CH$), 1.23 (3H, t, $J=7.0$ Hz, CH_3CH_2O), 0.97 (3H, d, $J=7.1$ Hz, $(CH_3)_2CH$), 0.93 (3H, d, $J=7.1$ Hz, $(CH_3)_2CH$). Consistent with literature.[25]

To (*S*)-(+)-valine ethyl ester hydrochloride (205 mg, 1.13 mmol) in THF (3 ml) at 0 °C under nitrogen was added triethylamine (315 µl, 2.26 mmol). After stirring for 5 min carbamoyl chloride **11** (526 mg, 1.13 mmol) in THF (2 ml) was added. After heating to 55 °C for 20 h the reaction was allowed to cool to room temperature and a white solid removed by filtration. The filtrate was purified by flash chromatography (5–20% EtOAc in petrol) to afford the title compound (*S*)-**27** (580 mg, 89%) as a colourless viscous oil, $[\alpha]_D^{20}$ +40.5 (*c* 3.9, $CHCl_3$); ν_{max}/cm^{-1} 3445, 3071, 2963, 2858, 2241, 1732, 1651, 1504, 1372, 1312, 1262, 1192, 1111, 823, 737, 505; δ_H (250 MHz, $CDCl_3$) 7.65–7.12 (15H, m, Ar-H), 4.94 (1H, d, $J=7.7$ Hz, NH), 4.67–4.52 (2H, m, PhC*H*C*H*), 4.38 (1H, dd, $J=7.7$, 4.7 Hz, ^iPrCH), 4.22–4.10 (2H, m, CH_3CH_2O), 2.46 (3H, s, NCH_3), 2.15–1.98 (1H, m, $(CH_3)_2CH$), 1.24 (3H, t, $J=7.1$ Hz, CH_3CH_2O), 0.97 (9H, s, $C(CH_3)_3$), 0.93–0.86 (6H, m, $(CH_3)_2CH$), 0.80 (3H, d, $J=6.5$ Hz, $NCHCH_3$); δ_C (75.4 MHz, $CDCl_3$, 1 aromatic CH not found) 172.8 (C), 157.6 (C), 141.5 (C), 135.7 (CH), 133.2 (C), 132.9 (C), 129.2 (CH), 128.9 (CH), 127.6 (CH), 127.4 (CH), 127.1 (CH), 127.0 (CH), 126.7 (CH), 77.0 (CH), 60.4 (CH_2), 58.2 (CH), 55.5 (CH), 31.0 (CH), 28.0 (CH_3), 26.6 (CH_3), 18.8 (C), 18.4 (CH_3), 17.8 (CH_3), 14.2 (CH_3), 13.8 (CH_3); *m/z* (CI, NH_3) 575 ($[M+H]^+$, 19%). Found: $[M+H]^+$, 575.3290. $C_{34}H_{47}N_2O_4Si$ requires 575.3305.

Ethyl N-(N-methyl-N-((1′S,2′S)-1′-TBDPSO-1′-phenyl-2′-propyl)carboxamido)-(R)-valinate ((*R*)-**27**). The above procedure using (*R*)-(−)-valine (118 mg, 1.0 mmol) afforded (*R*)-(−)-valine ethyl ester hydrochloride

(185 mg, 100%) as an off-white solid, δ_H (250 MHz, $CDCl_3$) 8.87 (2H, br s, NH_2), 4.37–4.19 (2H, m, CH_3CH_2O), 3.90 (1H, d, $J=4.8$ Hz, NCH), 2.49 (1H, m, $(CH_3)_2CH$), 1.31 (3H, t, $J=7.0$ Hz, CH_3CH_2O), 1.20–1.09 (6H, m, $(CH_3)_2CH$). Further reaction of (*R*)-(−)-valine ethyl ester hydrochloride (180 mg, 0.97 mmol) afforded the title compound (*R*)-**27** (420 mg, 78%) as a colourless viscous oil, $[\alpha]_D^{20}$ +37.3 (*c* 3.8, $CHCl_3$); ν_{max}/cm^{-1} 3438, 3071, 2963, 2858, 2242, 1731, 1650, 1503, 1372, 1311, 1262, 1195, 1111, 921, 823, 735, 703, 612; δ_H (250 MHz, $CDCl_3$) 7.65–7.10 (15H, m, Ar-H), 4.88 (1H, d, $J=7.7$ Hz, NH), 4.72–4.55 (1H, br m, PhCHC*H*), 4.50 (1H, d, $J=7.9$ Hz, PhC*H*CH), 4.43 (1H, dd, $J=7.7$, 4.7 Hz, ^{i}PrCH), 4.22–4.10 (2H, m, CH_3CH_2O), 2.34 (3H, s, NCH_3), 2.15–1.95 (1H, m, $(CH_3)_2CH$), 1.25 (3H, t, $J=7.0$ Hz, CH_3CH_2O), 0.93 (9H, s, $C(CH_3)_3$), 0.89 (3H, d, $J=6.9$ Hz, $(CH_3)_2CH$), 0.86 (3H, d, $J=6.9$ Hz, $(CH_3)_2CH$), 0.77 (3H, d, $J=6.6$ Hz, NCHCH_3); δ_C (62.9 MHz, $CDCl_3$, 3 aromatic CH not found) 172.8 (C), 157.7 (C), 141.6 (C), 135.7 (CH), 133.4 (C), 133.0 (C), 129.3 (CH), 129.1 (CH), 127.7 (CH), 127.2 (CH), 126.8 (CH), 77.0 (CH), 60.5 (CH_2), 58.1 (CH), 55.8 (CH), 31.4 (CH), 28.1 (CH_3), 26.6 (CH_3), 18.9 (C), 18.5 (CH_3), 17.7 (CH_3), 14.2 (CH_3), 14.0 (CH_3); *m/z* (CI, NH_3) 575 ($[M+H]^+$, 100%). Found: $[M+H]^+$, 575.3312. $C_{34}H_{47}N_2O_4Si$ requires 575.3305.

4.3.2.3. Attempted cleavage of the pseudoephedrine auxiliary. *Ethyl N-(N-methyl-N-((1′S,2′S)-1′-hydroxy-1′-phenyl-2′-propyl)carboxamido)-(S)-valinate* **29**. To a solution of TBDPS protected carboxamido valinate (*S*)-**27** (98 mg, 0.17 mmol) in THF (1.5 ml) was added 1 M TBAF in THF (0.3 ml, 0.3 mmol). After stirring at room temperature for 90 min, water (4 ml) was added and extracted with ether (2×5 ml). The organics were dried over $MgSO_4$, evaporated and purified by flash chromatography (2–5% MeOH in CH_2Cl_2) to afford the free-hydroxy carboxamido valinate **29** (55 mg, 96%) as a colourless viscous oil, $[\alpha]_D^{24}$ +56.0 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} 3323, 2966, 1733, 1632, 1518, 1454, 1394, 1314, 1260, 1191, 1028, 759, 702; δ_H (300 MHz, $CDCl_3$) 7.36–7.27 (5H, m, Ar-H), 5.24 (1H, d, $J=8.2$ Hz, NH), 4.52 (1H, dd, $J=8.5$, 5.1 Hz, PhC*H*CH), 4.40 (1H, dd, $J=8.4$, 4.8 Hz, ^{i}PrCH), 4.29–4.15 (4H, m, PhCHC*H*, OH, CH_3CH_2O), 2.82 (3H, s, NCH_3), 2.15 (1H, m, $(CH_3)_2CH$), 1.29 (3H, t, $J=7.1$ Hz, CH_3CH_2O), 1.00–0.92 (9H, m, $(CH_3)_2CH$ and NCHCH_3); δ_C (75.4 MHz, $CDCl_3$) 173.2 (C), 159.9 (C), 142.3 (C), 128.3 (CH), 127.6 (CH), 126.6 (CH), 76.8 (CH), 61.0 (CH_2), 58.5 (CH), 58.2 (CH), 31.2 (CH), 30.0 (CH_3), 19.0 (CH_3), 17.9 (CH_3), 15.1 (CH_3), 14.2 (CH_3); *m/z* (CI, NH_3) 337 ($[M+H]^+$, 100%). Found: $[M+H]^+$, 337.2123. $C_{18}H_{29}N_2O_4$ requires 337.2127.

N-(N-Methyl-N-((1′S,2′S)-1′-hydroxy-1′-phenyl-2′-propyl) carboxamido)-(S)-valine **30**. *Method A*. To a solution of free-hydroxy carboxamido valinate **29** (25 mg, 0.07 mmol) in THF (0.5 ml) and water (3 drops) was added lithium hydroxide monohydrate (3 mg, 0.07 mmol). After stirring at room temperature for 20 h the reaction mixture was partitioned between water (2 ml) and ether (4 ml). TLC analysis of the organic layer showed unreacted starting material **29**. The aqueous layer was acidified to pH∼2 with 2 M HCl and re-extracted with ether (4 ml). This organic layer was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to afford **30** as a colourless viscous oil (10 mg, 44%), $[\alpha]_D^{27}$ +40.0 (*c* 0.2, $CHCl_3$); ν_{max}/cm^{-1} 3377, 2966, 2606, 2248, 1723, 1611, 1525, 1396, 1203, 732; δ_H (250 MHz, $CDCl_3$) 7.36–7.26 (5H, m, Ar-H), 5.61 (1H, br d, $J=8.6$ Hz, NH), 4.52 (1H, d, $J=9.1$ Hz, PhCH), 4.29 (1H, dd, $J=8.6$, 5.2 Hz, ^{i}PrCH), 4.13 (1H, m, PhCHC*H*), 2.84 (3H, s, NCH_3), 2.22 (1H, m, $(CH_3)_2CH$), 1.08–0.90 (9H, m, NCHCH_3 and $(CH_3)_2CH$); δ_C (62.9 MHz, $CDCl_3$) 175.6 (C), 161.0 (C), 141.6 (C), 128.5 (CH), 127.9 (CH), 126.7 (CH), 76.3 (CH), 59.1 (CH), 58.7 (CH), 30.4 (CH), 29.6 (CH_3), 19.4 (CH_3), 18.0 (CH_3), 15.3 (CH_3); *m/z* (CI, NH_3) 309 ($[M+H]^+$, 10%). Found: $[M+H]^+$, 309.1812. $C_{16}H_{25}N_2O_4$ requires 309.1814.

Method B. To a solution of free-hydroxy carboxamido valinate **29** (30 mg, 0.09 mmol) in THF (0.5 ml) at 0 °C under nitrogen was added sodium hydride (60% w/w in mineral oil, 4 mg, 0.1 mmol). After stirring at room temperature for 20 h the reaction mixture was evaporated and partitioned between water (2 ml) and CH_2Cl_2 (4 ml). TLC analysis of the organic layer showed unreacted starting material **29**. The aqueous layer was acidified to pH∼2 with 2 M HCl and re-extracted with CH_2Cl_2 (4 ml). This organic layer was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to afford **30** as a colourless viscous oil (12 mg, 44%), analytically identical to that derived from method A.

Ethyl N-(((1′S,2′S)-2′-methylamino-1′-phenyl-1′-propyl) alkoxycarbonyl)-(S)-valinate hydrochloride **31**. To a sample of crude free-hydroxy carboxamido valinate **29**, derived from TBDPS protected carboxamido valinate **27** (166 mg, 0.29 mmol) without chromatographic purification, was added 1 M HCl in ether (2 ml, 2 mmol). After stirring under nitrogen at room temperature for 20 h, a white precipitate had formed which was removed by filtration and recrystallised from ethyl acetate to afford **31** (18 mg, 17%) as white needles, mp 145 °C (decomp.), $[\alpha]_D^{29}$ +31.6 (*c* 0.095, $CHCl_3$); ν_{max}/cm^{-1} 3372, 2967, 2736, 2459, 1729, 1529, 1467, 1375, 1270, 1233, 1209, 1095, 1028, 702; δ_H (250 MHz, $CDCl_3$) 9.94 and 9.72 (2H, 2×br, NH_2), 7.46–7.30 (5H, m, Ar-H), 6.39 (1H, d, $J=9.2$ Hz, NH), 5.47 (1H, d, $J=9.7$ Hz, PhCH), 4.20–4.00 (3H, m, ^{i}PrCH, CH_3CH_2O), 3.85–3.65 (1H, br m, PhCHC*H*), 2.67 (3H, br s, NCH_3), 2.30–2.10 (1H, m, $(CH_3)_2CH$), 1.24 (3H, d, $J=6.8$ Hz, NCHCH_3), 1.16 (3H, t, $J=7.0$ Hz, CH_3CH_2O), 1.02 (3H, d, $J=6.7$ Hz, $(CH_3)_2CH$), 1.00 (3H, d, $J=6.7$ Hz, $(CH_3)_2CH$); δ_C (62.9 MHz, $CDCl_3$) 171.4 (C), 154.6 (C), 136.3 (C), 129.2 (CH), 128.9 (CH), 127.1 (CH), 75.3 (CH), 60.9 (CH_2), 59.5 (CH), 57.1 (CH), 31.1 (CH), 27.1 (CH_3), 19.1 (CH_3), 17.8 (CH_3), 14.1 (CH_3), 12.3 (CH_3); *m/z* (CI, NH_3) 337 ($[M+H]^+$, 58%). Found: $[M+H]^+$, 337.2116. $C_{18}H_{29}N_2O_4$ requires 337.2127. The structure was confirmed by X-ray crystallography.[31]

The filtrate was shown by ^{1}H NMR to be predominantly unreacted free-hydroxy carboxamido valinate **27**.

4.3.3. Aminations using oxaziridine 4 (Tables 3–5).

4.3.3.1. General procedure. To a stirred solution of LiHMDS (1.0 M in hexanes, 0.22 ml, 0.22 mmol) in THF (1 ml) at −78 °C was added substrate (0.22 mmol) dropwise. After 30 min oxaziridine (65 mg, 0.22 mmol) in

THF (1 ml) was added dropwise. The reaction mixture was stirred at −78 °C for ca. 20 h before allowing to warm to room temperature. The reaction was quenched by the addition saturated aqueous NH_4Cl and CH_2Cl_2. The organic layer was further washed twice with saturated aqueous NH_4Cl, then dried (Na_2SO_4) and concentrated in vacuo. The product was then purified by flash chromatography.

4.3.3.2. Product data. *2-[N-(tert-Butylcarbonyl)amino] acetophenone* **32a**[27] (Table 3, entry 1). Using the above procedure followed by flash column chromatography (petrol–ethyl acetate 10:1) yielded the title compound (10.8 mg, 21%) as a white solid, mp 56.8–57.4 °C; δ_H (300 MHz, $CDCl_3$) 7.98 (2H, d, J=7.3 Hz, C*H*), 7.63 (1H, t, J=7.4 Hz, C*H*), 7.51 (2H, t, J=7.6 Hz, C*H*), 5.57 (1H, brd s, N*H*), 4.68 (2H, d, J=4.3 Hz, CH_2), 1.50 (9H, s, $(CH_3)_3$).

2-N-Boc-Amino-1-phenyl-1-propanone **32b**[28] (Table 3, entry 2). Using the above procedure followed by flash column chromatography (petrol–ethyl acetate 10:1) yielded the title compound (17 mg, 31%) as a white solid, mp 80.3–81.0 °C; δ_H (300 MHz, $CDCl_3$) 8.00 (2H, d, J=7.4 Hz, CH), 7.62 (1H, t, J=7.4 Hz, CH), 7.51 (2H, t, J=7.6 Hz, CH), 5.58 (1H, br s, NH), 5.32 (2H, app t, J=6.9 Hz, CH), 1.48 (9H, s, $(CH_3)_3$), 1.42 (3H, d, J=6.9 Hz, CH_3).

N-(2-Oxo-1,2-diphenyl-ethyl)-carbamic acid tertbutyl ester **32c**[29] (Table 3, entry 3). Using the above procedure followed by flash column chromatography yielded the title compound (10.2 mg, 15%) as a white solid, δ_H (300 MHz, $CDCl_3$) 7.98 (2H, d, J=7.4 Hz, CH), 7.52 (1H, t, J=7.3 Hz, CH), 7.26–7.44 (2H, m, CH), 6.29 (1H, d, J=7.6 Hz, CH), 6.04 (1H, d, J=7.6 Hz, NH), 1.45 (9H, s, $(CH_3)_3$).

(Cyano-phenyl-methyl)-carbamic acid tert-butyl ester **37a** (Table 4, entry 1). Using the above procedure followed by flash column chromatography (petrol–ethyl acetate 10:1) yielded the title compound (22.9 mg, 45%) as a white solid, mp 110.9–112.8 °C; ν_{max}(film)/cm^{-1} 3325, 2978, 1692; δ_H (300 MHz, $CDCl_3$) 7.44 (5H, m, ArC*H*), 5.82 (1H, d, J= 7.2 Hz, N*H*), 5.16 (1H, brd s, C*H*), 1.50 (9H, s, $(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 154.5 (C), 133.8 (C), 129.9 (CH), 129.7 (CH), 127.3 (CH), 118.1 (CN), 81.9 (C), 46.5(CH), 28.6 ($(CH_3)_3$); *m/z* (CI) 250 (M+NH_4), 233 (M+H). Found MH^+233.1282 $C_{13}H_{17}N_2O_2$ requires 233.1290.

[Cyano-(4-methoxy-δ-phenyl)-methyl]-carbamic acid tert-butyl ester ester **37b** (Table 4, entry 2). Using the above procedure followed by flash column chromatography (petrol–ethyl acetate 10:1) yielded the title compound (11.8 mg, 20%) as a white solid, mp 119.5–121.8 °C; ν_{max}(film)/cm^{-1} 3560, 3537, 2979, 2934, 2248, 1695, 1513; δ_H (300 MHz, $CDCl_3$) 7.41 (2H, d, J=8.6 Hz, ArC*H*), 6.95 (2H, d, J=8.7 Hz, ArC*H*), 5.73 (1H, brd d, J=7.3 Hz, N*H*), 5.07 (1H, brd s, 1H, C*H*), 3.84 (3H, s, OCH_3), 1.49 (9H, s, $(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 160.4 (C), 154.1 (C), 128.4 (C*H*), 125.5 (C), 117.9 (CN), 114.6 (CH), 81.5 (C), 55.4 (OCH_3), 45.7 (CH), 28.2 ($(CH_3)_3$); *m/z* (CI) 280 (M+NH_4), 263 (M+H). Found (M+NH_4), 280.1665. $C_{14}H_{22}N_3O_3$ requires 280.1661.

[(4-Chloro-phenyl)-cyano-methyl]-carbamic acid tert-butyl ester **37c** (Table 4, entry 3). Using the above procedure followed by flash column chromatography (petrol–ethyl acetate 10:1) yielded the title compound (26.8 mg, 46%) as a white solid, mp 143.8–144.7 °C; ν_{max}(film)/cm^{-1} 3432, 3055, 2988, 2306, 1721; δ_H (300 MHz, $CDCl_3$) 7.42–7.43 (4H, m, ArC*H*), 5.80 (1H, brd d, 1H, J=6.9 Hz, N*H*), 5.24 (1H, brd d, J=6.9 Hz, C*H*), 1.49 (9H, s, $(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 154.1 (C), 135.5 (C), 132.0 (C), 129.4 (CH), 128.2 (CH), 117.3 (CN), 81.7 (C), 45.4 (CH), 28.2 ($(CH_3)_3$); *m/z* (CI) 284 (M+NH_4), 267 (M+H). Found MH^+267.0903. $C_{13}H_{15}N_2O_2Cl$ requires 267.0900.

tert-Butoxycarbonylaminocyano acetic acid ethyl ester ester **37d** (Table 4, entry 4). Using the above procedure followed by flash column chromatography (petrol–ethyl acetate 10:1) yielded the title compound (16.5 mg, 33%) as a white solid, mp 69.8–72.0 °C; ν_{max}(film)/cm^{-1} 3344, 2985, 2932, 2254, 1753, 1684; δ_H (300 MHz, $CDCl_3$) 5.47 (1H, brd d, J=6.6 Hz, N*H*), 5.23 (1H, d, J=7.9 Hz, C*H*), 4.37 (3H, q, J=7.1 Hz, CH_2), 1.48 (9H, s, $(CH_3)_3$) 1.37 (3H, t, J=7.1 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 163.6 (C), 154.1 (C), 114.4 (CN), 82.0 (C), 64.1 (CH_2), 44.7 (CH), 28.1 ($(CH_3)_3$) 13.9 (CH_3); *m/z* (CI) 246 (M+NH_4), 229 (M+H). Found MH^+229.1186. $C_{10}H_{17}N_2O_4$ requires 229.1188.

The same reaction with 1.5 equiv **4** gave **37d** (13.1 mg, 26%) as a white solid and the diaminated species (14.1 mg 18%) as a white solid, mp 125–127 °C. Diaminated (di-*tert*-butoxycarbonylamino)cyano acetic acid ethyl ester, ν_{max}(film)/cm^{-1} 3323, 3272, 2980, 2929, 1764, 1698, 1685; δ_H (300 MHz, $CDCl_3$) 6.43 (2H, brd s, $(NH)_2$), 4.44 (2H, q, J=7.1 Hz, CH_2CH_3), 1.47 (9H, s, $(CH_3)_3$), 1.37 (3H, t, J=7.1 Hz, CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 162.9 (C), 153.4 (C), 114.1 (CN), 82.7 (C), 65.3 (CH_2), 62.4 (C), 28.5 ($(CH_3)_3$) 14.1 (CH_3); *m/z* (CI) 361 (M+NH_4), 344 (M+H). Found MH^+344.1810. $C_{15}H_{26}N_3O_6$ requires 344.1822.

tert-Butoxycarbonylaminocyano acetic acid tert-butyl ester **37e** (Table 4, entry 5). Using the above procedure followed by flash column chromatography (petrol–ethyl acetate 10:1) yielded the title compound (11.6 mg, 20%) as an oil; ν_{max}(film)/cm^{-1} 3352, 2981, 2934, 2254, 1815, 1749, 1722, 1152; δ_H (300 MHz, $CDCl_3$) 5.37 (1H, s, N*H*), 5.16 (1H, d, J=7.9 Hz, C*H*), 1.55 (9H, s, $(CH_3)_3$) 1.49 (9H, s, $(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 162.2 (C), 154.0 (C), 114.7 (CN), 86.0 (C), 81.8 (C), 45.1 (CH) 28.1 ($(CH_3)_3$), 27.7 ($(CH_3)_3$); *m/z* (CI) 274 (M+NH_4), 257 (M+H). Found M+NH_4 274.1760. $C_{12}H_{24}N_3O_4$ requires 274.1767.

tert-Butoxycarbonylaminocyanophenyl acetic acid ethyl ester **37f** (Table 4, entry 6). Using the above procedure but using 1.5 equiv oxaziridine (95 mg, 0.33 mmol) followed by flash column chromatography (petrol–ethyl acetate 10:1) yielded the title compound (46.9 mg, 70%) as an oil; ν_{max}(film)/cm^{-1} 3416, 3060, 2983, 2937, 2253, 1754, 1721, 1481, 1286; δ_H (300 MHz, $CDCl_3$) 7.67 (2H, br s, C*H*), 7.45–7.46 (3H, m, C*H*), 5.75 (1H, br s, N*H*), 4.29 (2H, q, J=7.2 Hz, CH_2), 1.46 (9H, s, $(CH_3)_3$) 1.25 (3H, t, J=7.2 Hz); δ_C (75 MHz, $CDCl_3$, 323 K) 165.4 (C), 160.9 (C), 133.6 (C), 129.9 (CH), 129.2 (CH), 125.9 (CH), 116.2 (CN), 82.2 (C), 64.1 (CH_2) 61.4 (C), 28.1 ($(CH_3)_3$) 13.6 (CH_3); *m/z* (CI) 322 (M+NH_4), 305 (M+H). Found MH^+305.1511. $C_{16}H_{21}N_2O_4$ requires 305.1501.

Dimethyl-2-[(tert-butyloxycarbonyl)amino]methylmalonate **38a** (Table 5, entry 1). Using the above procedure (anion stirred with the oxaziridine for 4 h) followed by flash column chromatography (petrol–ethyl acetate 10:1) yielded the title compound (17.2 mg, 30%) as an oil; ν_{max}(film)/cm^{-1} 3432, 2978, 2957, 1746, 1720, 1288; δ_H (300 MHz, $CDCl_3$) 5.94 (1H, s, N*H*), 3.79 (6H, s, (OCH_3)$_2$), 1.75 (3H, s, CH_3), 1.44 (9H, s, (CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 167.6 (C), 152.1 (C), 78.6 (C), 61.1 (C), 51.6 (OCH$_3$)$_2$) 26.4 ((CH$_3$)$_3$), 19.9 (CH$_3$); *m/z* (CI) 279 (M+NH$_4$), 262 (M+H). Found MH$^+$262.1302. $C_{11}H_{20}NO_6$ requires 262.1290.

Diethyl-2-[(tert-butyloxycarbonyl)amino]methylmalonate **37f** (Table 5, entry 2). Using the above procedure followed by flash column chromatography (petrol–ethyl acetate 10:1) yielded the title compound (13.8 mg, 22%) as an oil, ν_{max}(film)/cm^{-1} 3432, 2980, 2939, 1741, 1721, 1283; δ_H (300 MHz, $CDCl_3$) 5.91 (1H, s, N*H*), 4.25 (4H, q, J=7.0 Hz, (OCH_2CH$_3$)$_2$), 1.74 (3H, s, CH_3), 1.44 (9H, s, (CH_3)$_3$) 1.27 (6H, t, J=7.0 Hz, (OCH$_2$CH_3)$_2$); δ_C (75 MHz, $CDCl_3$) 167.8 (C), 152.8 (C), 79.2 (C), 61.9 (C), 61.3 (CH$_2$), 27.2 (CH$_3$)$_3$), 20.4 (CH$_3$), 12.9 (CH$_3$); *m/z* (CI) 307 (M+NH$_4$), 290 (M+H). Found M+NH$_4$ 290.1596. $C_{13}H_{24}NO_6$ requires 290.1604.

4.3.4. α-Chlorination of titanium enolates. *α-Chloropropiophenone* **33**.[21] To a solution of propiophenone (70 μl, 0.52 mmol) in CH_2Cl_2 (2 ml) at −78 °C under nitrogen was added titanium tetrachloride (70 μl, 0.64 mmol) followed by tributylamine (175 μl, 0.74 mmol). After stirring for 30 min oxaziridine **3a** (150 mg, 0.59 mmol) in CH_2Cl_2 (1 ml) was added. The reaction was allowed to warm to room temperature over 2.5 h, quenched with saturated aqueous NH_4Cl (15 ml), and extracted with CH_2Cl_2 (3×10 ml). The combined organics were dried over $MgSO_4$, filtered, evaporated and purified by flash chromatography (5% EtOAc in petrol) to afford α-chloropropiophenone **33** (74 mg, 84%) as a yellow oil, δ_H (250 MHz, $CDCl_3$) 8.00–7.95 (2H, m, Ar-H), 7.60–7.41 (3H, m, Ar-H), 5.24 (1H, q, J=6.7 Hz, CH), 1.71 (3H, d, J=6.7 Hz, CH_3); *m/z* (CI, NH_3) 186 ([M+NH$_4$]$^+$, 95%). Consistent with literature.[21]

Similar reaction of propiophenone (18 μl, 0.13 mmol) with oxaziridine **8** (~95%, 90 mg, 0.15 mmol) afforded α-chloropropiophenone **33** (3 mg, 13%), analytically identical to above. HPLC analysis (Chiralcel-OD, 0.5 ml/min, 1% ^{i}PrOH in hexane) showed racemic product.

α-Chlorodeoxybenzoin **34**.[21] Reaction of deoxybenzoin (99 mg, 0.5 mmol) as above afforded α-chlorodeoxybenzoin **346** (100 mg, 86%) as a white solid, δ_H (250 MHz, $CDCl_3$) 8.02–7.30 (10H, m, Ar-H), 6.36 (1H, s, CH); *m/z* (CI, NH_3) 248 ([M+NH$_4$]$^+$, 100%). Consistent with literature.[21]

4.3.5. Reaction of ethyl phenylcyanoacetate with 2-(diethylcarboxamido)-3-(*p*-chlorophenyl)oxaziridine 3a using LiHMDS as base. Reaction of ethyl phenylcyanoacetate (36 μl, 0.20 mmol), oxaziridine **3a** (51 mg, 0.20 mmol) and LiHMDS (1 M in hexanes, 200 μl, 0.20 mmol) followed by flash chromatography (4–40% EtOAc in petrol) afforded ethyl phenylketoacetate **35** (16 mg, 45%) and α-cyano-*N*-diethylcarboxamido-*p*-chlorobenzylamine **36** (16 mg, 30%).

Ethyl phenylketoacetate **35**.[26] Isolated as a colourless oil, δ_H (250 MHz, $CDCl_3$) 8.01 (2H, m, Ar-H), 7.66 (1H, tt, J=7.3, 1.6 Hz, Ar-H), 7.51 (2H, m, Ar-H), 4.45 (2H, q, J=7.1 Hz, OCH_2CH$_3$), 1.42 (3H, t, J=7.1 Hz, OCH$_2$CH_3). Consistent with lit.[26]

α-Cyano-N-diethylcarboxamido-p-chlorobenzylamine **36**. Isolated as an off-white solid, ν_{max}/cm^{-1} 3315, 2977, 2933, 1637, 1518, 1492, 1282, 1094, 826; δ_H (250 MHz, $CDCl_3$) 7.48–7.36 (4H, m, Ar-H), 6.10 (1H, d, J=8.6 Hz, CH), 5.03 (1H, br d, J=8.6 Hz, NH), 3.34–3.19 (4H, m, NCH_2CH$_3$), 1.14 (6H, t, J=7.2 Hz, NCH$_2$CH_3); δ_C (101 MHz, $CDCl_3$) 155.1 (C), 135.2 (C), 133.0 (C), 129.4 (CH), 128.3 (CH), 118.2 (C), 45.3 (CH), 41.4 (CH$_2$), 13.7 (CH$_3$); *m/z* (CI, NH_3) 283 ([M+NH$_4$]$^+$, 97%), 266 ([M+H]$^+$, 100). Found: [M+H]$^+$, 266.1066. $C_{13}H_{17}N_3OCl$ requires 266.1060.

4.3.6. Reaction of acetophenone-trimethylsilylenol ether with oxaziridine 3a. A solution of acetophenone TMS enol ether (80 μl, 0.39 mmol) and oxaziridine **1a** (90 mg, 0.35 mmol) in ethanol (0.4 ml) was stirred at room temperature under nitrogen. After 44 h, 1 M HCl (2 ml) was added and extracted with CH_2Cl_2 (2×2 ml). The organics were dried over $MgSO_4$, filtered and evaporated to afford a crude mixture of amino ester **41** and hydroxy ketone **40** (~1:8). α-Hydroxyacetophenone **40** was isolated as a white solid, δ_H (250 MHz, $CDCl_3$) 7.92 (2H, m, Ar-H), 7.63 (1H, m, Ar-H), 7.50 (2H, m, Ar-H), 4.88 (2H, d, J=4.7 Hz, CH_2), 3.53 (1H, t, J=4.7 Hz, OH). Consistent with literature.[30] Amidoketone **41** was not isolated in pure form, but was identified by the following data: δ_H (250 MHz, $CDCl_3$) includes 5.54 (1H, br m, NH), 4.82 (2H, d, J=4.2 Hz, CH_2); *m/z* (CI, NH_3) 235 ([M+H]$^+$, 100%). Found: [M+H]$^+$, 235.1447. $C_{13}H_{19}N_2O_2$ requires 235.1447.

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References and notes

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