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Studies on the Lewis acid mediated cleavage of α-aminoacetals: synthesis of novel 1,2-aminoethers, and evidence for α-alkoxy aziridinium ion intermediates †

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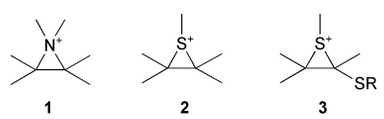
The nucleophilic cleavage of α-amino acetals induced by TMSOTf can be used to prepare a wide range of substituted 1,2-aminoethers. In particular, organometallic reagents, N-heterocycles, and enamines all react efficiently to give products in good yield. In appropriate cases, good levels of stereocontrol are possible, but this is very dependent on the nature of the nucleophile and the substrate, with diethylzinc proving particularly effective across a range of substrates. The degree of stereocontrol can be used to infer the nature of the reactive intermediates involved in the reaction. With diethylzinc, it is most likely that the reaction proceeds by coordination of the nucleophile to the amino group followed by transfer of an ethyl group to an α-oxocarbenium ion. With non-coordinating nucleophiles, the stereochemical outcome can be rationalised in terms of addition to the possible α-alkoxy aziridinium ion intermediates.

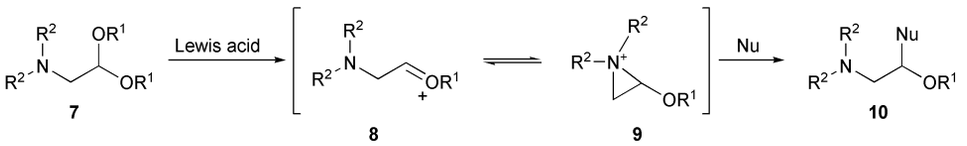
Introduction

The development of new chemistry based on reactive intermediates such as aziridinium ions (**1**) and episulfonium ions (**2**) continues to be an important area of research.[1,2] These are now well-established synthetic intermediates, allowing access to highly functionalised products, often with a high degree of stereochemical control. In the course of our own studies in this area,[3] we have recently begun to investigate new methods for the generation of related reactive intermediates containing further heteroatom substituents, to investigate their reactivity and synthetic utility. We have recently demonstrated the intermediacy of α-thio episulfonium ions (**3**) by consideration of the stereochemical outcome of the Lewis acid mediated cleavage of α-acetoxy sulfides, prepared in an enantiomerically enriched form by enzymatic resolution.[4] Related intermediates have been proposed during the preparation of α-sulfenyl dithioacetals,[5] but have otherwise been little investigated. The related α-alkoxy episulfonium ions (**4**) and related intermediates have been the subject of more detailed investigations, although in some cases, it would appear that the corresponding open chain α-oxocarbenium ion (*cf.* **8**, Scheme 1) is a more likely intermediate.[6] In the case of the corresponding nitrogen systems, α-alkoxy aziridinium ions (**5**) are potentially very useful synthetic intermediates, but appear not to have been investigated to a significant degree.[7] The related α-alkoxy aziridines (**6**) are better established, being formed by the addition of alkoxides to azirines, or by aziridination of enol ethers.[8] However, even these species, which one would expect to be relatively stable compared to the aziridinium derivatives, are difficult to isolate unless there are particular stabilising influences, and are usually reacted further prior to product isolation. It is thus unlikely that α-alkoxy aziridinium ions (**5**) would be isolable, but their presence as reactive intermediates is not unreasonable.



On reaction with appropriate nucleophiles, α-alkoxy aziridinium ions would, in principle, allow access to 1,2-amino ethers with a high degree of stereochemical control (Scheme 1). However, the reaction is more complex in that there is also the potential for the α-alkoxy aziridinium ion (**9**) to be in equilibrium with an open chain α-oxocarbenium ion (**8**) or various intermediate forms. This could have important effects on the reactivity and stereochemical outcome of the reaction with nucleophiles. We envisaged that such effects would be important, and might allow us to be able to differentiate between the possible reaction pathways to determine the nature of the reactive intermediate involved. Hence this work is of mechanistic interest, particularly if reaction pathways involving either **8** or **9** could be distinguished, but also synthetically important due to the potential for the formation of a variety of highly functionalised 1,2-amino alcohols and derivatives thereof, which often show interesting biological activity.[9]

† Electronic supplementary information (ESI) available: correlation of ^{1}H NMR spectra between the *syn* and *anti* diastereomeric series. See http://www.rsc.org/suppdata/ob/b2/b210116e/



Scheme 1

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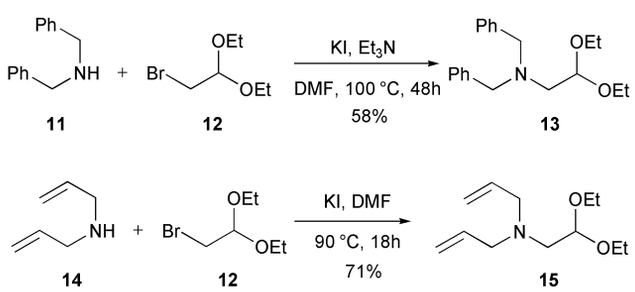
We thus embarked on a research programme to investigate the reactivities of intermediates such as **8** and **9**, and to exploit them in the area of stereocontrolled synthesis. This paper discusses the results of this study in detail.

Initial investigations

In principle, α-alkoxy aziridinium ions (**9**) and related intermediates can be generated by Lewis acid mediated cleavage of α-amino acetals (**7**), and our initial goal was to demonstrate feasibility of this process (Scheme 1).[10] Synthesis of substrates for investigation was readily accomplished by reacting the required secondary amine (diallylamine, dibenzylamine) with bromoacetaldehyde diethyl acetal in DMF at 90–100 °C in the presence of catalytic potassium iodide (Scheme 2). Substituents on nitrogen were chosen such that they would allow subsequent deprotection to the corresponding primary amine if required, which we considered important to enhance the versatility of the methodology.[11] Interestingly, dibenzylamine was considerably less reactive than diallylamine in this reaction, an observation which would have implications for the synthesis of more substituted systems (*vide infra*).



Scheme 2

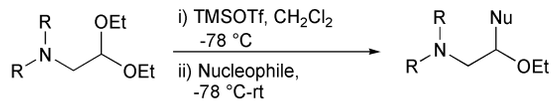
We then investigated the Lewis acid mediated nucleophilic cleavage of these simple acetals. Treatment of the substrates with trimethylsilyl trifluoromethanesulfonate (TMSOTf) at −78 °C followed by addition of the nucleophile and slowly warming to room temperature gave good yields of the acetal substitution products **16**–**19** (Table 1).

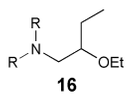
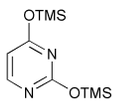
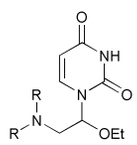
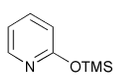
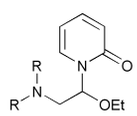
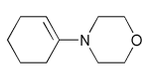
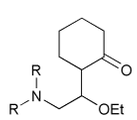
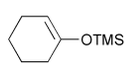
Reaction with organometallic species such as dialkylzinc and Grignard reagents proceeded efficiently, for both the *N*-allyl[12] and *N*-benzyl substrates (entries 1–3 in Table 1). Similarly, introduction of the uracil group and 2-pyridone was also efficient (entries 4–7). Enamines reacted smoothly to introduce carbonyl functionality (entry 8), but with silyl enol ethers, the Lewis acidic reaction conditions led to further loss of ethanol to give the αβ-unsaturated ketone as the major product (entry 9).

Reactions of acetals derived from (*R,R*)-(−)-bis(α-methylbenzyl)amine

These encouraging preliminary results led us to consider investigating more complex systems which had greater potential for stereocontrolled synthesis. As a simple extension to the above, we decided to synthesise the (*R,R*)-(−)-bis(α-methylbenzyl)amine derivative **20** which we reasoned may have the potential for controlling the stereochemistry at the new chiral centre, particularly if the reaction proceeded via the α-alkoxy aziridinium ion. Use of the previous methodology (Scheme 2) for the synthesis of **20** was unsuccessful (<5% yield) alongside related alternative procedures, presumably due to the very much greater steric hindrance around the amino group. Instead, a reductive amination procedure was adopted utilising commercially available glyoxal-1,1-dimethylacetal, (*R,R*)-(−)-bis(α-methylbenzyl)amine, and sodium triacetoxyborohydride (Scheme 3).[13] Even in this case, a 3:1 mixture of products was

Table 1 TMSOTf mediated nucleophilic cleavage of α-amino acetals



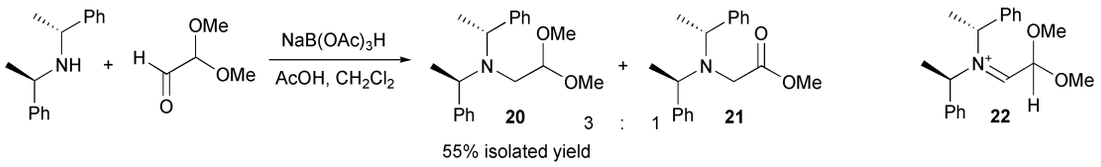
Entry	R	Nucleophile	Product	Yield (%)
1	Bn	Et_2Zn	 **16**	86
2	Allyl	Et_2Zn		65
3	Bn	EtMgBr		71
4	Allyl		 **17**	75
5	Bn			77
6	Allyl		 **18**	64
7	Bn			84
8	Bn		 **19**	86[a]
9	Bn			13[ab]

[a] 78:22 mixture of isomers; [b] Major product (57%) is enone from further loss of EtOH.

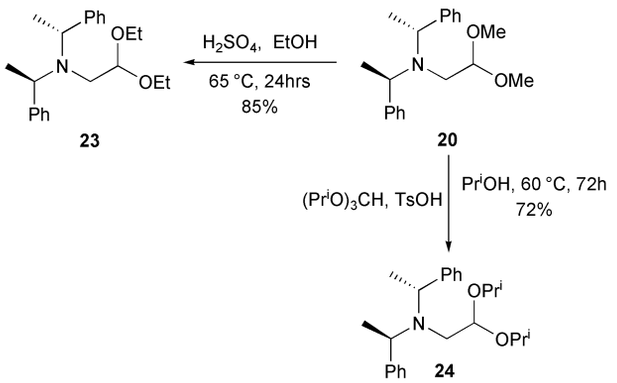
formed in favour of **20**, with the ester (**21**) presumably resulting from 1,2-hydride migration in the iminium ion intermediate (**22**) also being formed. This was readily removed however, by basic hydrolysis and aqueous extraction, leaving a 55% isolated yield of the desired acetal (**20**).

We believed the nature of the acetal group may be an important factor in influencing the stereocontrol in this reaction, hence we also prepared both the ethyl acetal (**23**) and isopropyl acetal (**24**) by acid catalysed exchange (Scheme 4). In the case of the diethyl acetal, this was readily achieved using ethanol and sulfuric acid, however in the case of the isopropyl system analogous conditions led only to isolation of the original amine, either by hydride migration and hydrolysis of the intermediate iminium ion, or elimination of methanol and hydrolysis of the resultant enamine. Fortunately the use of tri(isopropyl)orthoformate and *p*-TsOH gave clean acetal exchange with the desired product (**24**) isolated in 72% yield.

The nucleophilic cleavage of these acetals was then investigated (Table 2). All nucleophiles reacted efficiently to give good yields of products, however stereocontrol proved to be very variable, depending on the nature of the nucleophile employed. Diethylzinc showed the highest selectivity, giving **25** as an 85:15 ratio of diastereoisomers, irrespective of the nature of the acetal (entries 1, 2 and 4). The more sterically demanding diisopropylzinc afforded the product **26** with low stereoselectivity (entry 5). Disappointingly, other organometallic reagents such as Grignards and organocuprates also gave only modest stereocontrol (entries 2, 6 and 7), as was also the case for the heterocyclic nucleophiles bis(*O*-trimethylsilyl)uracil and 2-(trimethylsilyloxy)pyridine (entries 8, 9 and 10), and an enamine (entry 11). With indole as nucleophile, the only acetal-derived product (**31**) was that where two equivalents of the



Scheme 3



Scheme 4

indole had added to the acetal (entry 12). This was not unsurprising considering the known lability of related systems under Lewis acidic conditions.[14] The yield for formation of **31** could be optimised to 64% if five equivalents of indole were used. Also formed in this reaction was 2-(3-indolyl)indoline,[15] a known by-product of indole dimerisation under acidic reaction conditions.

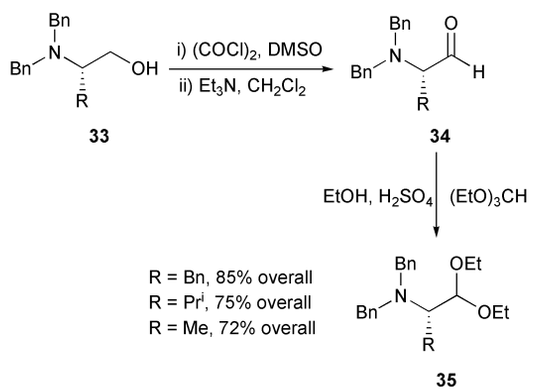
In the absence of nucleophiles, an interesting cyclisation is observed, most likely originating from attack of an intermediate α-oxocarbenium ion (*cf.* **8**) onto the adjacent aromatic ring to form the tetrahydroisoquinoline **32**.[16] Interestingly, this reaction gave the highest diastereoselectivity (80% de) in this series.

All of the above reactions were carried out at −78 °C; the temperature was maintained at this level during the addition of TMSOTf and the nucleophile, then for a further 2–3 h before gradual warming to room temperature. Studies with the heterocyclic nucleophiles to improve the stereochemical control in the reaction by altering the length of time before or after the addition of the nucleophile, showed no significant effect. Attempted initiation of the reaction using TBDMSOTf in place of TMSOTf simply led to recovery of starting material.

Our results showed that the stereoselectivity of the acetal cleavage reaction was dependent on the nature of the nucleophile. It was however surprising that changing the nature of the acetal resulted in no significant improvement in selectivity for either the organometallic (entries 1, 3 and 4) or heterocyclic (entries 8 and 9) nucleophiles. This suggested a rethink of the methodology was required if more useful levels of stereocontrol were going to be realised.

Reaction of α-aminoacetals derived from chiral 1,2-amino alcohols

Although our early results demonstrated that some stereochemical control was possible, with the exception of reactions of diethyl zinc, these were generally modest at best. One possible reason for this may be that the stereocontrolling element is too remote from the new chiral centre. A potentially more promising system may be to have stereocontrolling element adjacent to the developing chiral centre. Thus a further series of α-aminoacetals were synthesised derived from chiral 1,2-amino alcohols.[17] The substrates were synthesised from the corresponding optically active, commercially available *N*,*N*-dibenzyl-1,2-amino alcohols (**33**) by Swern oxidation, and immediate acetal formation from the crude aldehydes using ethanol and triethylorthoformate under acid catalysis (Scheme 5). The stereochemical integrity of acetal (**35** R = Bn) was confirmed by ^{1}H NMR using the chiral shift reagent Eu(hfc)$_3$ which showed that no appreciable racemisation of the intermediate aldehyde (**34** R = Bn) had occurred (e.e. >95%).[18]



Scheme 5

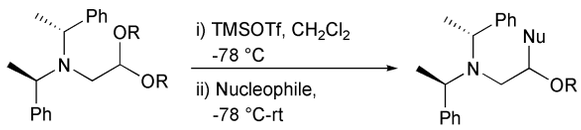
These substrates were then subjected to the same reaction conditions as before. The results of these reactions are shown in Table 3 and show that all reactions proceed efficiently in good to excellent yields. A number of interesting trends should also be noted. Firstly, as previously observed, the use of diethylzinc as nucleophile gave the product **36** with the highest levels of diastereoselectivity; in this case this was the case irrespective of size of the substituent R (entries 1, 2 and 3). Secondly, when R is large (Bn, Pr^i) high levels of selectivity are obtained, irrespective of the nucleophile (entries 1, 2, 4, 5 and 7). Thirdly, low selectivity is observed with the heterocyclic nucleophiles with a small R group (Me) in the substrate (entries 6 and 8).

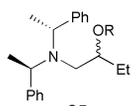
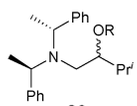
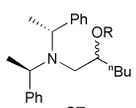
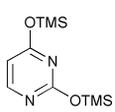
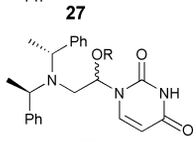
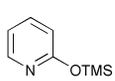
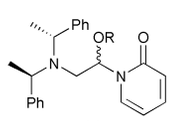
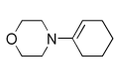
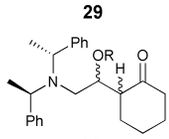
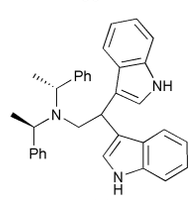
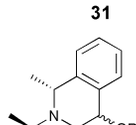
Having obtained appreciable levels of stereocontrol, the stereochemical assignments for the major products of the reaction became of prime importance. The addition of diethyl zinc to the aldehyde (**34** R = Bn) is reported to give the *syn* diastereomer **39** as the major product (Scheme 6) on the basis of ^{1}H NMR coupling constants in the oxazolidinone product **40**.[19] Repeating the preparation of **39** and converting the major product to the ethyl ether gives **41**, which by comparison of spectroscopic data, was shown to be the minor isomer formed in our reactions. This leads to the *anti* assignment for the major products for the addition of diethyl zinc to acetals **35** (Table 3, entries 1, 2 and 3). The stereochemistry of the uracil derivative **37** (R = Bn) (Table 3, entry 4) was determined by X-ray crystallography (Figure 1), which clearly shows the *syn* stereochemistry.[10]

Further evidence for stereochemical assignment comes from comparison of a range of ^{1}H NMR chemical shifts of the products. For all examples where comparative data is available,[20] there is a good correlation between the *syn* and *anti* diastereomeric series.

The most remarkable aspect of these stereochemical assignments is that they show that for all the reactions investigated, the sense of stereoselection is reversed when switching from diethyl zinc to the nitrogen heterocycles. These intriguing observations, in keeping with our original aims of the research (*vide supra*), allow considerable insight into the nature of the

Table 2 TMSOTf mediated nucleophilic cleavage of acetals derived from bis(α-methylbenzyl)amine



Entry	Nucleophile	R	Major product	Diast. ratio[a]	Yield (%)
1	Et_2	Me	 **25**	85 : 15	67
2	EtMgBr	Me		64 : 36	87
3	Et_2Zn	Et		85 : 15	73
4	Et_2Zn	Pr^i		85 : 15	72
5	$Pr^i{}_2Zn$	Me	 **26**	55 : 45	53
6	Pr^iMgCl	Me		62 : 38	77
7	Bu_2CuLi	Me	 **27**	62 : 38	72
8		Me	 **28**	55 : 45	85
9		Pr^i		55 : 45	76
10		Me	 **29**	70 : 30	82
11		Me	 **30**	13 : 6 : 4 : 2	86
12		Me	 **31**		64[b]
13	None[c]	Me	 **32**	90 : 10	69

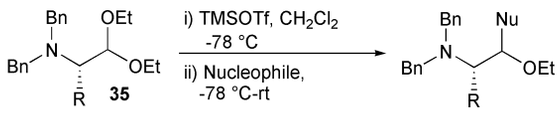
[a] Configuration of major isomer not determined. [b] Five equivalents of indole used. [c] Reaction left for 3 d at rt.

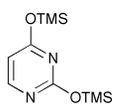
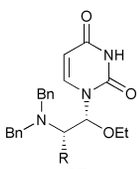
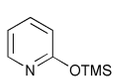
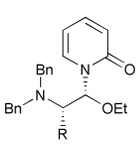
reactive intermediates involved and are worthy of further mechanistic discussion.

Mechanistic aspects

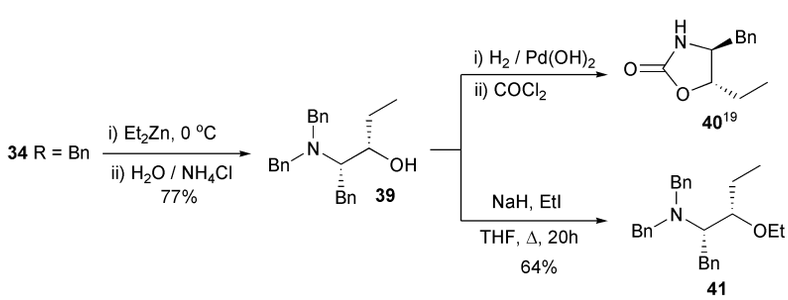
The Lewis acid mediated nucleophilic cleavage of acetals is a reaction of considerable mechanistic and synthetic interest. The nature of the reactive species involved is determined by an intricate balance of electronic and steric effects, and reaction conditions.[21] Further evidence for this is provided by our own work described here, where both the nature of the nucleophile and the substrate substituents can have a significant influence on the stereochemical outcome of the reaction. The good levels of stereoselectivity consistently observed when using diethyl zinc with a wide variety of acetals are particularly notable (Tables 2 and 3), and suggest that the mechanism of the reaction may have significant differences to that for other nucleophiles. For example, it is well established that organozinc reagents are generally quite unreactive organometallic reagents towards carbonyl compounds unless activated by coordination to a tertiary amine or alkoxide.[22] In this case, although the α-oxocarbenium ion would be expected to be significantly more reactive than simple aldehydes, the organozinc reagent may still require some degree of activation. It is thus likely that the reaction proceeds *via* pre-coordination of the diethyl zinc to the tertiary amine group within the substrate (e.g. **46**, Scheme 7). This leads to an

Table 3 TMSOTf mediated nucleophilic cleavage of chiral α-amino acetals



Entry	R	Nucleophile	Major product	Diast. ratio	Yield (%)
1	Bn	Et_2Zn	 **36**	95 : 5[a]	64
2	Pr^i	Et_2Zn		93 : 7	61
3	Me	Et_2Zn		94 : 6	77
4	Bn		 **37**	>95 : 5[b]	70
5	Pr^i			89 : 11	78
6	Me			55 : 45	71
7	Bn		 **38**	95 : 5	89
8	Me			54 : 46	87

[a] Stereochemical assignment confirmed by comparison with literature (Scheme 1).[19] [b] Stereochemical assignment confirmed by X-ray crystallography (Figure 1).[10]



Scheme 6

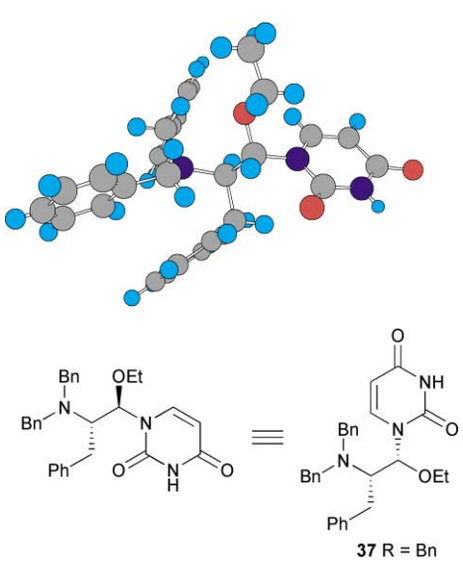
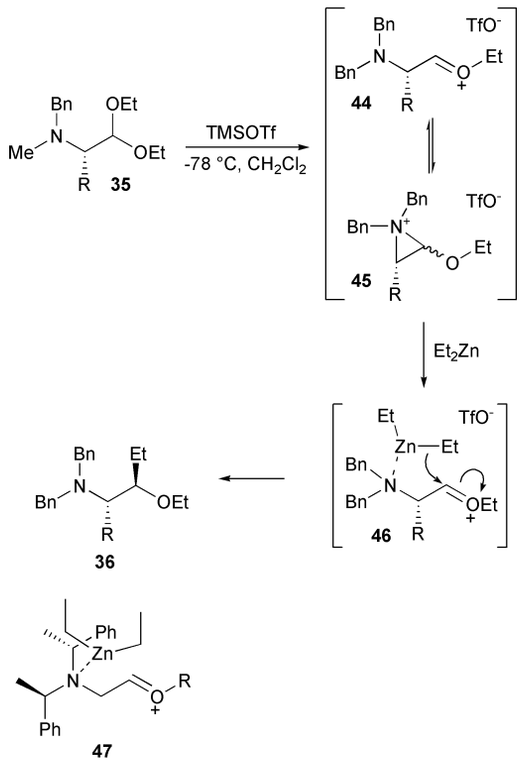


Fig. 1 X-Ray crystal structure of **37** (R = Bn).

exaggeration of steric effects around the reacting centre and could also lead to 'intramolecular' delivery of the ethyl group, both of which would be expected to result in increased levels of selectivity. Importantly, because the nitrogen atom is now coordinated to zinc, it is no longer able to stabilise the adjacent cationic centre, and so it would not be expected to be able to form an α-alkoxy aziridinium ion intermediate (e.g. **45**), and the reaction proceeds via an α-oxocarbenium ion (**44**). In such a case, the nature of the acetal groups would be expected to have minimal effect on selectivity, as they are remote from the reacting centre. This is consistent with the reactions of the various acetals derived from bis(α-methylbenzyl)amine (Table 2) where almost identical good levels of selectivity were observed with Et_2Zn irrespective of the size of the acetal group (Me, Et and Pr^i). In such a case, an intermediate such as **47** may be expected, where in addition, coordination of Et_2Zn helps relay the stereochemical information from the otherwise remote chiral centres on the α-methylbenzylamine moieties to the developing chiral centre, leading to the reasonable selectivities observed. We have so far been unable to establish the stereochemical outcome of these particular reactions, however we do not believe this detracts significantly from the mechanistic discussion.

In the case of the nitrogen heterocycles, the situation would appear to be significantly more complex. Acetals derived from α-methylbenzylamine (Table 2) show only low selectivity at best. There are two possible explanations for this. Firstly, there are two possible diastereomeric α-alkoxy aziridinium ions **48** and **50** (probably equilibrating via a low concentration of the



Scheme 7

α-oxocarbenium ion **49**), which would, assuming a stereocontrolled S_N2-like ring opening, each lead to the formation of one of the possible diastereomeric products, **51** and **52** respectively (Scheme 8). However, it would be expected that the energy difference between these two possible intermediates would be relatively small as the chiral centres in the α-methylbenzylamine group are rather distant from the new aziridinium chiral centre. Hence a mixture of the 2 isomeric α-alkoxy aziridinium ions **48** and **50** would be formed, leading to a corresponding mixture of diastereomeric products **51** and **52**. An alternative explanation is that attack of the external nucleophile occurs directly on the α-oxocarbenium ion intermediate **49**. Such attack would be remote to any stereocontrolling elements leading to formation of a mixture of products.

Similar considerations can be applied to rationalise the more complex results obtained with the chiral amino acetals **35** described in Table 3. Although the variable levels of selectivity observed may be expected and are consistent with the size of the substituents R, the predominant *syn* stereoselectivity is unlikely to originate from addition to the α-oxocarbenium ion **54**. Indeed, the Felkin–Anh model (Fig. 2) would predict formation of **57**, the minor product in all cases, and this is usually particularly strong for such heteroatom containing systems.[23] Detailed studies by Reetz and others have shown that *anti*

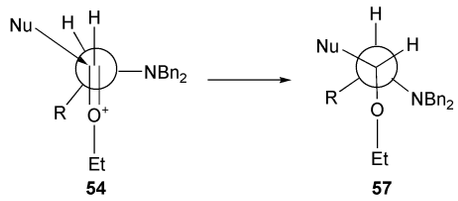
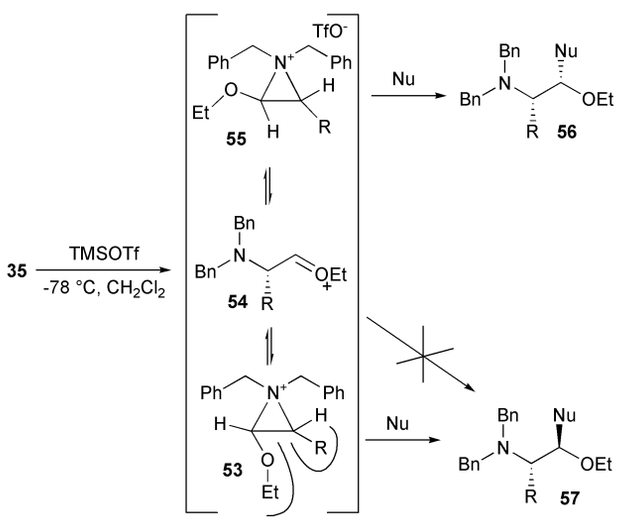


Fig. 2 Felkin–Anh model predicts formation of **57** for addition to α-oxocarbenium ion **54**.

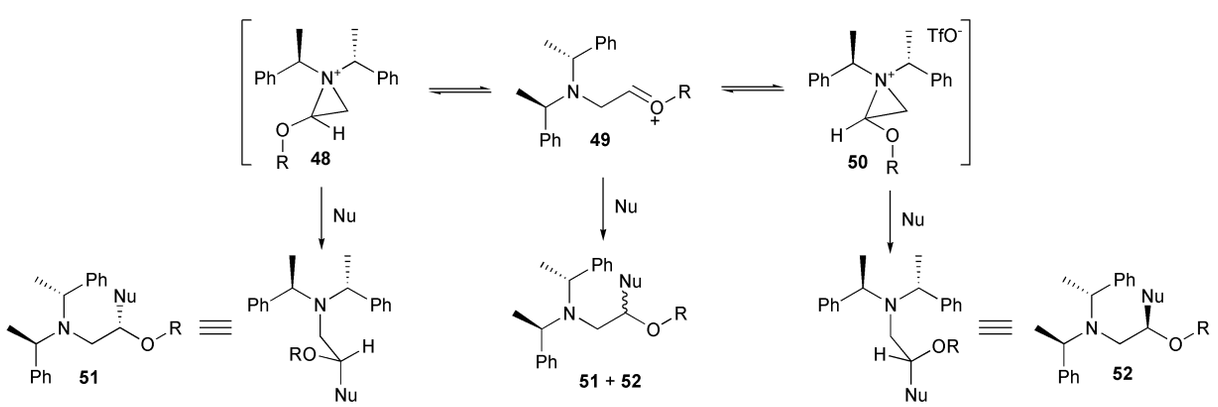
selectivity is predominant in the reaction of chiral α-amino aldehydes with a variety of organometallic nucleophiles.[17]

Again, the relative stability of the various possible α-alkoxy aziridinium ions can be invoked to explain the observations (Scheme 9). There are two possible isomeric α-alkoxy aziridinium intermediates we can form, the cis (**53**) and trans (**55**) isomers, which may be in equilibrium *via* a small concentration of the α-oxocarbenium ion (**54**). Extensive broadening observed during variable temperature ^{1}H NMR experiments on intermediates derived from **35** (R = Bn) suggest this, but other processes such as acetal exchange, which may also be expected to lead to significant broadening, cannot be discounted.



Scheme 9

Stereocontrolled S_N2-like nucleophilic ring opening of the *trans* isomer **55** would give the observed *syn* product, whereas the *cis* isomer **53** would give the *anti* product. For large substituents (R = Bn, Pr^i), the *cis* aziridinium ion **53** would be expected to be significantly less stable than the trans **55** due to a steric clash between adjacent substituents on the three-membered ring. This leads to the high *syn* selectivity observed with these substituents. The fact that little or no *anti* product is formed suggests that direct addition to the α-oxocarbenium ion



Scheme 8

54 does not occur. With smaller substituents (R = Me) there would be much less difference in energy between the *cis* and *trans* isomeric aziridinium ions **53** and **55**, and hence both would be present in similar concentrations leading to the mixtures of products observed.

Although much of the evidence for α-alkoxy aziridinium ions described here is circumstantial, their intermediacy, particularly at low temperatures is not unrealistic, and provides what we believe to be the first real evidence for these potentially interesting and useful reactive intermediates. We now aim to exploit these results further in the stereocontrolled synthesis of important biologically active molecules.

In summary, we have demonstrated that nucleophilic cleavage of acetals induced by TMSOTf can be used to prepare a wide range of substituted 1,2-aminoethers. In particular, organometallic reagents, N-heterocycles, and enamines all react efficiently to give products in good yield. In appropriate cases, good levels of stereocontrol are possible, but this is very dependent on the nature of the nucleophile and the substrate, with diethylzinc proving particularly effective. The degree of stereocontrol can be used to infer the nature of the reactive intermediates involved in the reaction. With diethylzinc, it is most likely that the reaction proceeds by addition of a coordinated zinc species to an α-oxocarbenium ion, whereas with non-coordinating nucleophiles, the stereochemical outcome is consistent with addition to an α-alkoxy aziridinium ion.

Experimental section

General procedures and instrumentation

Nuclear magnetic resonance spectra were recorded at 500MHz for ^{1}H or 125MHz for ^{13}C on a Bruker DRX 500 spectrometer, or at 300MHz for ^{1}H or 75MHz for ^{13}C on a Bruker DPX 300 machine. ^{1}H chemical shifts are expressed in parts per million (ppm) downfield of tetramethylsilane, and ^{13}C chemical shifts are expressed in ppm referenced to the central peak of the triplet of deuterated chloroform (77.0 ppm). All coupling constants are quoted in hertz (Hz), (multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; sept, septet; m, multiplet). 2D COSY spectra were used to assign complex ^{1}H NMR spectra, and DEPT and HMQC techniques assisted in the assignment of ^{13}C spectra.

Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR ESP spectrometer. Only the most significant absorptions are listed. Mass spectra were recorded on a VG Autospec mass spectrometer for electron impact (EI) and fast atom bombardment (FAB) spectra. Electrospray (ES) spectra were recorded on a Micromass LCT K111 spectrometer. Molecular ions are reported as mass with percentage abundance quoted in brackets. Optical rotations were recorded on an Optical Activity AA-100 polarimeter as a solution in chloroform with the concentration quoted in brackets (g (100 ml)$^{-1}$). Melting points were determined on a Reichert Hot Stage apparatus and are uncorrected. Microanalyses were carried out at the University of Leeds Microanalytical laboratory. All C, H and N analytical figures are expressed in percentage values of total molecular weight. HPLC was carried out on a Gynotek GINA50 machine. Thin layer chromatography (tlc) was carried out using precoated plastic backed silica plates, which were visualized using ultraviolet light or potassium permanganate stain.[24] Column chromatography was carried out on Merck silica gel (230–400 mesh) unless otherwise stated. Petroleum ether was distilled in the range 40–60 °C.

All reactions were carried out at atmospheric pressure under a positive pressure of dry, oxygen-free nitrogen. Solvents were removed under reduced pressure using a Büchi rotary evaporator at water aspirator pressure, followed by drying under high vacuum at 0.1 Torr. Solvents were purified before use using established procedures.[25] Dichloromethane and *N*,*N*-dimethylformamide (DMF) were distilled over calcium hydride before use, and THF was distilled over sodium and benzophenone. Bis(*O*-trimethylsilyl)uracil,[26] 2-(trimethylsilyloxy)-pyridine,[27] and 1-morpholinocyclohexane[28] were prepared according to literature procedures.

Synthesis and reactions of achiral α-amino acetals (Scheme 2 and Table 1)

***N*,*N*-Dibenzyl)aminoacetaldehyde diethyl acetal, 13.** To a solution of bromoacetaldehyde diethyl acetal (3.05 ml, 4.00 g, 20.3 mmol) in DMF (30 ml) was added dibenzylamine (3.90 ml, 4.00 g, 20.3 mmol), triethylamine (3.40 ml, 2.46 g, 24.3 mmol) and potassium iodide (1.68 g, 10.2 mmol). The mixture was heated at 100 °C for 2 d, then water (70 ml) was added, and the product extracted with diethyl ether (3 × 80 ml), then dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified by silica gel flash chromatography (eluent: petroleum ether/ethyl acetate/triethylamine 89 : 10 : 1) to yield the *acetal* **13** as a pale yellow oil (3.69 g, 11.8 mmol, 58%). δ_H (400 MHz, $CDCl_3$), 1.20 (3H, t, *J* 7.0, OCH_2CH_3), 1.21 (3H, t, *J* 7.0, OCH_2CH_3), 2.70 (2H, d, *J* 4.9, $NCH_2CH(OEt)_2$), 3.48 (2H, dq, *J* 9.1, 7.0, OCH_2CH_3), 3.60 (2H, dq, *J* 9.1, 7.0, OCH_2CH_3), 3.71 (4H, s, NCH_2Ph), 4.62 (1H, t, *J* 4.9, $CH(OEt)_2$), 7.24–7.43 (10H, m, Ph); δ_C (75 MHz, $CDCl_3$), 15.3 (OCH_2CH_3), 55.9 ($NCH_2CH(OEt)_2$), 59.0 (NCH_2Ph), 61.8 (OCH_2CH_3), 102.2 ($CH(OEt)_2$), 126.8 (Ph), 128.1 (Ph), 128.8 (Ph), 139.7 (Ph); IR (neat), ν_{max}/cm^{-1} 2970, 2880, 2791, 1444, 1375, 1112, 1060, 745, 695; MS (FAB) *m*/*z* 313 (M + 1, 15%), 312 (37), 268 (37), 210 (100), 91 (85); Microanalysis: found C 76.8, H 8.5, N 4.35; calculated for $C_{20}H_{27}NO_2$: C 76.64, H 8.68, N 4.47.

(*N*,*N*-Diallyl)aminoacetaldehyde diethyl acetal, 15. To a solution of bromoacetaldehyde diethyl acetal (15.3 ml, 20.0 g, 101 mmol) in DMF (100 ml) was added diallylamine (25.1 ml, 19.7 g, 203 mmol) and potassium iodide (8.47 g, 50.7 mmol). The mixture was heated at 90 °C for 18 h, then water (120 ml) was added, and the product extracted with diethyl ether (3 × 150 ml). The organic extracts were washed with brine (100 ml), then dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified by silica gel flash chromatography (eluent: petroleum ether/ethyl acetate/triethylamine 89 : 10 : 1) to yield the *acetal* **15** as a pale yellow oil (15.3 g, 71.9 mmol, 71%). δ_H(300 MHz, $CDCl_3$), 1.18 (6H, t, *J* 7.1, $(OCH_2CH_3)_2$), 2.58 (2H, d, *J* 5.3, $NCH_2CH(OEt)_2$), 3.14 (4H, dt, *J* 6.5, 1.2, $N(CH_2CH{=}CH_2)_2$), 3.49 (2H, dq, *J* 9.3, 7.1, $(OCH_2CH_3)_2$), 3.64 (2H, dq, *J* 9.3, 7.1, $(OCH_2CH_3)_2$), 4.48 (1H, t, *J* 5.3, $CH(OEt)_2$), 5.07–5.16 (4H, m, $N(CH_2CH{=}CH_2)_2$), 5.77–5.87 (2H, m, $N(CH_2CH{=}CH_2)_2$); δ_C (75 MHz, $CDCl_3$), 15.3 ($(OCH_2CH_3)_2$), 55.5 ($NCH_2CH(OEt)_2$), 57.7 ($N(CH_2CH{=}CH_2)_2$), 61.9 ($OCH_2CH_3)_2$), 102.1 ($CH(OEt)_2$), 117.3 ($N(CH_2CH{=}CH_2)_2$), 135.7 ($N(CH_2CH{=}CH_2)_2$); IR (neat), ν_{max}/cm^{-1} 2961, 2910, 2880, 2790, 1441, 1418, 1369, 1128, 1057, 1021, 994, 912; MS (EI) *m*/*z* 213 (M^+, 1%), 168 (17), 110 (100), 103 (21), 75 (15); Microanalysis: found C 67.4, H 11.0, N 6.6; calculated for $C_{12}H_{23}NO_2$: C 67.57, H 10.87, N 6.57.

Typical procedure A

(*N*,*N*-Dibenzyl)-1-amino-2-ethoxybutane, 16 (R = Bn). TMSOTf (521 μl, 640 mg, 2.88 mmol) was added to a stirred solution of (*N*,*N*-dibenzyl)aminoacetaldehyde diethyl acetal (301 mg, 960 μmol) in CH_2Cl_2 (7 ml) at −78 °C. The temperature was maintained at –78 °C for 30 min, then diethyl zinc (1.1 M solution in toluene, 1.73 ml, 237 mg, 1.92 mmol) was added. The mixture was stirred at −78 °C for a further 2 h, then gradually warmed to room temperature. After 14 h, $NaHCO_3$ (sat. aq., 20 ml) was added, the product extracted with CH_2Cl_2 (3 × 25 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified by silica gel flash chromatography (eluent: petroleum ether/ethyl acetate/triethylamine 96 : 3 : 1), to yield

the *ether* **16** (R = Bn) as a colourless oil (246 mg, 827 μmol, 86%). δ_H (300 MHz, $CDCl_3$), 0.75 (3H, t, *J* 7.4, CH(OEt)-CH_2CH_3), 1.15 (3H, t, *J* 7.0, OCH_2CH_3), 1.38 (1H, quin, *J* 7.1, CH(OEt)CH_2CH_3), 1.51–1.63 (1H, m, CH(OEt)CH_2CH_3), 2.49 (2H, app. t, *J* 5.9, NCH_2CH(OEt)Et), 3.29 (1H, quin, *J* 5.9, NCH_2CH(OEt)Et), 3.40–3.53 (2H, m, CH(OCH_2CH_3)Et), 3.53 (2H, d, *J* 13.8, N($CH_2Ph)_2$), 3.65 (2H, d, *J* 13.6, N($CH_2Ph)_2$), 7.18–7.38 (10H, m, Ph); δ_C (75 MHz, $CDCl_3$), 9.9 ($CH(OEt)CH_2CH_3$), 16.1 (OCH_2CH_3), 25.9 ($CH(OEt)CH_2$-CH_3), 57.5 (NCH_2CH(OEt)Et), 59.8 (N($CH_2Ph)_2$), 65.1 (OCH_2CH_3), 79.7 (NCH_2CH(OEt)Et), 127.2 (Ph), 128.5 (Ph), 129.3 (Ph), 140.2 (Ph); IR (neat), ν_{max}/cm^{-1} 2971, 2928, 2874, 2795, 1495, 1453, 1110, 1072, 747, 698; MS (EI) *m*/*z* 297 (M^+, 5%), 211 (19), 210 (83), 181 (8), 91 (100); Microanalysis: found C 80.85, H 9.2, N 4.55; calculated for $C_{20}H_{27}NO$: C 80.76, H 9.15, N 4.71.

(*N*,*N*-Diallyl)-1-amino-2-ethoxybutane 16 (R = allyl). Typical procedure A was used with TMSOTf (297 μl, 1.64 mmol), (*N*,*N*-diallyl)-aminoacetaldehyde diethylacetal (100 mg, 469 mol) and diethylzinc (1.0 M solution in hexanes, 1.40 ml, 1.40 mmol). The product was purified by silica gel flash chromatography (eluent: petroleum ether/ethyl acetate 98 : 2) to yield the *ether* **16** (R = allyl) as a colourless oil (60 mg, 305 μmol, 65%); δ_H(500 MHz, $CDCl_3$), 0.90 (3 H, t, *J* 7.2, $CH(OEt)CH_2CH_3$), 1.18 (3 H, t, *J* 7.2, OCH_2CH_3), 1.44 (1H, ddq, *J* 14.2, 7.1 and 7.1, CH(OEt)CH_2CH_3), 1.58 (1H, ddq, *J* 14.2, 5.1 and 7.1, CH(OEt)CH_2CH_3), 2.44 (1 H, dd, *J* 13.3 and 5.8, NCH_2CH-(OEt)Et), 2.50 (1 H, dd, *J* 13.3 and 5.8, NCH_2CH(OEt)Et), 3.08 (2 H, dd, *J* 14.1 and 6.4, N(CH_2CH=$CH_2)_2$), 3.15 (2 H, dd, *J* 14.1 and 6.4, N(CH_2CH=$CH_2)_2$), 3.28 (1 H, quin. *J* 5.8, C*H*(OEt)Et), 3.50 (1 H, dq, *J* 9.3 and 7.0, OCH_2CH_3), 3.57 (1 H, dq, *J* 9.3 and 7.0, OCH_2CH_3), 5.11 (2 H, dd, *J* 10.2 and 1.5, N(CH_2CH=C$H_2)_2$), 5.16 (2 H, dd, *J* 17.0 and 1.5, N(CH_2-CH=C$H_2)_2$), 5.85 (2 H, ddt, *J* 17.0, 10.2 and 6.4, N(CH_2-C*H*=$CH_2)_2$); δ_C (75 MHz, $CDCl_3$), 10.1 ($CH(OEt)CH_2CH_3$), 16.1 (OCH_2CH_3), 26.1 ($CH(OEt)CH_2CH_3$), 57.1 (NCH_2-CH(OEt)Et), 58.3 (N(CH_2CH=$CH_2)_2$), 65.2 (OCH_2CH_3), 79.7 (*C*H(OEt)Et), 117.6 (N(CH_2CH=$CH_2)_2$), 136.4 N(CH_2-*C*H=$CH_2)_2$); IR (neat) ν_{max}/cm^{-1} 3079, 2929, 1643; MS (ES) *m*/*z* (%) 198 (100, M^+ + H); Microanalysis: found C 72.8, H 11.65, N 7.2; calculated for $C_{12}H_{23}NO$: C 73.0, H 11.75, N 7.1.

Typical procedure B

1-((*N*,*N*-Diallylamino)ethoxyethyl)-1*H*-pyrimidine-2,4-dione, 17 (R = allyl). TMSOTf (722 μl, 886 mg, 3.99 mmol) was added to a stirred solution of (*N*,*N*-dibenzyl)aminoacetaldehyde diethyl acetal (709 mg, 3.32 mmol) in CH_2Cl_2 (7 ml) at −78 °C. The temperature was maintained at −78 °C for 30 min, then bis(*O*-trimethylsilyl)uracil (1.70g, 6.64 mmol) was added. The mixture was stirred at −78 °C for a further 2 h, then warmed to room temperature. After 20 h at ambient temperature, a saturated solution of sodium hydrogen carbonate (20 ml) was added, the product extracted with CH_2Cl_2 (3 × 25 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified by silica gel flash chromatography (eluent: petroleum ether/ethyl acetate/triethylamine 50 : 49 : 1 to ethyl acetate), to yield the *uracil derivative* **17** (R = allyl) (696 mg, 2.49 mmol, 75%) as a colourless oil. δ_H (300 MHz, $CDCl_3$), 1.18 (3H, t, *J* 7.0, OCH_2CH_3), 2.69 (2H, d, *J* 5.9, NCH_2CH(OEt)N), 3.05 (2H, dd, *J* 13.9, 6.9, N(CH_2CH=$CH_2)_2$), 3.15 (2H, dd, *J* 13.9, 6.0, N(CH_2CH=$CH_2)_2$), 3.51 (2H, q, *J* 7.0, OCH_2CH_3), 5.08–5.14 (4H, m, (NCH_2CH=C$H_2)_2$), 5.63–5.66 (1H, m, NCH_2CH(OEt)N), 5.65–5.81 (2H, m, (NCH_2CH=$CH_2)_2$), 5.76 (1H, d, *J* 8.0, *uracil*–C*H*), 7.34 (1H, d, *J* 8.0, *uracil*–C*H*), 9.35 (1H, s, br, *uracil*–N*H*); δ_C (75 MHz, $CDCl_3$), 15.2 (OCH_2CH_3), 55.6 (NCH_2-CH(OEt)N), 58.1 (N(CH_2CH=$CH_2)_2$), 65.4 (OCH_2CH_3), 83.4 (NCH_2CH(OEt)N), 102.4 (*uracil*–*C*H), 118.3 ((N(CH_2CH=$CH_2)_2$), 135.6 (((N(CH_2CH=$CH_2)_2$), 140.5 (*uracil*–*C*H), 151.6 (*uracil*–*C*O), 164.0 (*uracil*–*C*O); IR (neat), ν_{max}/cm^{-1} 2905, 2855, 1661, 1448, 1268, 1240, 1162, 1031; MS (EI) *m*/*z* 282 (M^+3, 1%), 279 (0.2), 169 (26), 110 (100), 98 (15), 70 (49).

1-((*N*,*N*-Dibenzylamino)-ethoxyethyl)-1*H*-pyrimidine-2,4-dione, 17 (R = Bn). Typical procedure B was used with TMSOTf (537 μl, 659 mg, 2.97 mmol), (*N*,*N*-dibenzyl)-aminoacetaldehyde diethyl acetal (310 mg, 989 μmol) and bis(*O*-trimethylsilyl)uracil (380 mg, 1.48 mmol). After 20 h at ambient temperature, the reaction was worked up as described and the product purified by silica gel flash chromatography (eluent: petroleum ether/ethyl acetate/triethylamine 50 : 49 : 1), to yield the *uracil derivative* **17** (R = Bn) as colourless plates (288 mg, 759 μmol, 77%). M.p. 135–138 °C; δ_H (300 MHz, $CDCl_3$), 1.17 (3H, t, *J* 7.0, OCH_2CH_3), 2.72 (2H, d, *J* 6.0, NCH_2CH), 3.40 (2H, d, *J* 13.2, NCH_2Ph), 3.48 (2H, q, *J* 7.0, OCH_2CH_3), 3.78 (2H, d, *J* 13.2, NCH_2Ph), 5.49 (1H, d, *J* 8.1, *uracil*–C*H*), 5.86 (1H, t, *J* 6.0, NCH_2CH(OEt)N), 6.88 (1H, d, *J* 8.1, *uracil*–C*H*), 7.21–7.28 (10H, m, Ph); δ_C (75 MHz, $CDCl_3$), 15.3 (OCH_2CH_3), 55.9 (NCH_2CH), 59.5 (NCH_2Ph), 65.3 (OCH_2-CH_3), 83.1 (NCH_2CH(OEt)N), 102.7 (*uracil*–*C*H), 127.6 (Ph), 128.8 (Ph), 129.5 (Ph), 139.0 (Ph), 139.8 (*uracil*–*C*H), 151.7 (*uracil*–*C*O), 164.0 (*uracil*–*C*O); IR (nujol mull), ν_{max}/cm^{-1} 2919(s), 2852, 1697, 1683, 1448, 1383, 1257, 1081, 749, 698; MS (EI) *m*/*z* 380 (M + 1, 0.8%), 211 (49), 210 (100), 206 (22), 92 (38), 91 (95), 65 (36); Microanalysis: found C 69.45, H 6.65, N 11.1; calculated for $C_{22}H_{25}N_3O_3$: C 69.64, H 6.64, N 11.07.

1-((*N*,*N*-Diallylamino)ethoxyethyl)-1*H*-pyridin-2-one, 18 (R = allyl). Typical procedure B was used with TMSOTf (207 μl, 254 mg, 1.14 mmol), (*N*,*N*-diallyl)aminoacetaldehyde diethyl acetal (222 mg, 1.04 mmol), and 2-(trimethylsilyloxy)pyridine (261 mg, 1.56 mmol). The product was purified by silica gel flash chromatography (eluent: petroleum ether/ethyl acetate/triethylamine 50 : 49 : 1), to yield *the pyridone* **18** (R = allyl) as a pale yellow oil (175 mg, 670 μmol, 64%). δ_H (300 MHz, $CDCl_3$), 1.19 (3H, t, *J* 7.0, OCH_2CH_3), 2.73 (1H, d, *J* 3.7, NCH_2CH-(OEt)N), 2.75 (1H, d, *J* 4.5, NCH_2CH(OEt)N), 3.17 (4H, dt, *J* 6.4, 1.2, N(CH_2CH=$CH_2)_2$), 3.43 (1H, dq, *J* 9.5, 7.0, OCH_2CH_3), 3.52 (1H, dq, *J* 9.6, 7.0, OCH_2CH_3), 5.07–5.18 (4H, m, N(CH_2CH=C$H_2)_2$), 5.66–5.80 (2H, m, N(CH_2-C*H*=$CH_2)_2$), 6.16–6.20 (1H, m, NCH_2CH(OEt)N), 6.23 (1H, dd, *J* 6.7, 1.2, *py*5–C*H*), 6.52 (1H, ddd, *J* 9.1, 1.2, 0.7, *py*3–C*H*), 7.32 (1H, ddd, *J* 9.1, 6.5, 2.1, *py*4–C*H*), 7.46 (1H, ddd, *J* 7.0, 2.1, 0.6, *py*6–C*H*); δ_C (75 MHz, $CDCl_3$), 15.3 (OCH_2CH_3), 56.5 (NCH_2CH(OEt)N), 57.9 (N(CH_2CH=$CH_2)_2$), 65.3 (OCH_2CH_3), 83.7 (NCH_2CH(OEt)N), 106.1 (*py*5–*C*H), 118.0 (N(CH_2CH=$CH_2)_2$), 120.9 (*py*3–*C*H), 133.1 (*py*4–*C*H), 135.9 (N(CH_2CH=$CH_2)_2$), 139.7 (*py*6–*C*H), 163.2 (*py*2–*C*O); IR (neat), ν_{max}/ cm^{-1} 2972, 2895, 2805, 1636, 1579, 1554, 1528, 1250, 1236, 1148, 1135, 1101, 1084, 990, 916, 761; MS (EI) *m*/*z* 262 (M^+, 0.1%), 221 (2), 167 (22), 110 (100).

1-((*N*,*N*-Dibenzylamino)-ethoxyethyl)-1*H*-pyridin-2-one, 18 (R = Bn). Typical procedure B was used with TMSOTf (330 μl, 406 mg, 1.83 mmol), (*N*,*N*-dibenzyl)aminoacetaldehyde diethyl acetal (477 mg, 1.52 mmol), and 2-(trimethylsilyloxy)pyridine (381 mg, 2.28 mmol). The product was purified by silica gel flash chromatography (eluent: petroleum ether/ethyl acetate/triethylamine 50 : 49 : 1), to yield *the pyridone* **18** (R = Bn) as a colourless oil (463 mg, 1.27 mmol, 84%). δ_H (300 MHz, $CDCl_3$), 1.16 (3H, t, *J* 7.0, CH_2CH_3), 2.77 (2H, d, *J* 5.9, 3.2, NCH_2CH), 3.48 (2H, dq, *J* 9.5, 7.0, CH_2CH_3), 3.55 (2H, d, *J* 13.6, NCH_2Ph), 3.77 (2H, d, *J* 13.6, NCH_2Ph), 6.10 (1H, dt, *J* 1.1, 5.6, *py*5–C*H*), 6.35 (1H, t, *J* 5.9, NCH_2CH), 6.53 (1H, dt, *J* 9.2, 0.6, *py*3–C*H*), 7.15–7.35 (12H, m, Ph, *py*4–C*H*, *py*6–C*H*); δ_C (300 MHz, $CDCl_3$), 15.4 (OCH_2CH_3), 57.0 (NCH_2CH), 59.1 (NCH_2Ph), 65.2 (OCH_2CH_3), 82.7 (NCH_2CH(OEt)N), 106.3 (*py*5–*C*H), 120.9 (*py*3–*C*H), 127.3 (Ph), 128.6 (*py*4–*C*H),128.8 (Ph), 129.3 (Ph), 133.0 (*py*6–*C*H), 139.5 (Ph), 140.5 (*py*2–*C*O);

IR (neat), ν_{max}/cm^{-1} 3050, 3031, 2978, 2920(s), 2801, 1651, 1575, 1535, 1490, 1448, 1370, 1240, 1145, 1095, 1028, 748, 698; MS (EI) *m/z* 362 (M$^+$, 0.4%), 361 (1), 317 (2), 267 (45), 238 (10), 210 (75), 176 (12), 92 (25), 91 (100); Microanalysis: found C 75.5, H 6.95, N 7.3; calculated for $C_{23}H_{26}N_2O_2$: C 75.61, H 7.12, N 7.6.

Typical procedure C

1-(*N*,*N*-Dibenzyl)amino-2-(2-oxocyclohexyl)-2-ethoxyethane, 19 (R = Bn). TMSOTf (520 μl, 638 mg, 2.87 mmol) was added to a stirred solution of (*N*,*N*-dibenzyl)aminoacetaldehyde diethyl acetal (300 mg, 957 μmol) in CH_2Cl_2 (7 ml) at −78 °C. The temperature was maintained at −78 °C for 30 min, then 1-morpholinocyclohexene (160 mg, 957 μmol) was added. The mixture was stirred at −78 °C for a further 2 h, then warmed to room temperature. After 30 min, water (10 ml) was added and the mixture stirred vigorously for 40 min, then a saturated solution of sodium hydrogen carbonate (20 ml) was added, the product extracted with CH_2Cl_2 (3 × 25 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified by silica gel flash chromatography (eluent: petroleum ether/ethyl acetate/triethylamine 89 : 10 : 1), to yield *the ketone* **19** (R = Bn) as a colourless oil and an inseparable mixture of two diastereoisomers (299 mg, 818 μmol, 86%). HPLC (eluent hexane/2-propanol) indicated a 78 : 22 mixture of diastereoisomers. Major diastereoisomer: δ_H (500 MHz, $CDCl_3$), 1.10 (3H, t, *J* 7.0, OCH_2CH_3), 1.30–1.38 (1H, m, *cyclohexyl*–$H6_{ax}$), 1.35–1.43 (1H, m, *cyclohexyl*–$H5_{ax}$), 1.46–1.50 (1H, m, *cyclohexyl*–$H6_{eq}$), 1.53–1.63 (1H, m, *cyclohexyl*–$H4_{ax}$), 1.69–1.73 (1H, m, *cyclohexyl*–$H5_{eq}$), 1.93–1.98 (1H, m, *cyclohexyl*–$H4_{eq}$), 2.22 (1H, dddd, *J* 14.2, 12.9, 6.1, 1.1, *cyclohexyl*–$H3_{ax}$), 2.36 (1H, dddd, *J* 14.2, 4.8, 3.3, 1.6, *cyclohexyl*–$H3_{eq}$), 2.44 (1H, dd, *J* 13.0, 5.5, $NCH_2CH(OEt)$), 2.47 (1H, dd, *J* 13.0, 7.9, $NCH_2CH(OEt)$), 2.52–2.57 (1H, m, *cyclohexyl*–$H2_{ax}$), 3.43 (2H, d, *J* 13.4, $N(CH_2Ph)_2$), 3.48 (1H, dq, *J* 9.2, 7.0, OCH_2CH_3), 3.62 (1H, dq, *J* 9.2, 7.0, OCH_2CH_3), 3.68 (2H, d, *J* 13.4, $N(CH_2Ph)_2$), 4.07 (1H, ddd, *J* 8.1, 5.4, 3.4, $NCH_2CH(OEt)$), 7.20–7.32 (10H, m, $N(CH_2Ph)_2$); δ_C (125 MHz, $CDCl_3$), 15.6 (OCH_2CH_3), 24.7 (*cyclohexyl*–C5), 25.9 (*cyclohexyl*–C4), 26.8 (1H, m, *cyclohexyl*–C6), 42.2 (*cyclohexyl*–C3), 52.0 (*cyclohexyl*–C1), 54.4 ($NCH_2CH(OEt)$), 59.3 ($N(CH_2Ph)_2$), 66.0 (OCH_2CH_3), 73.6 ($NCH_2CH(OEt)$), 127.0 (Ph), 128.2 (Ph), 129.1 (Ph), 139.5 (Ph), 212.1 (*cyclohexyl*–C2); Mixture of diastereoisomers: IR (neat), ν_{max}/cm^{-1} 1706, 1445, 1266, 1103, 1072, 740, 700; MS (FAB) *m/z* 366 (M + 1, 23%), 365 (M$^+$, 10%), 364 (32), 320 (7), 288 (4), 211 (17), 210 (98), 91 (100); Microanalysis: found C 78.6, H 8.5, N 3.9; calculated for $C_{24}H_{31}NO_2$: C 78.86, H 8.55, N 3.83.

(*E*)-2-(2-(*N*,*N*-Dibenzylamino)ethylidene)cyclohexanone (Table 1, entry 9). TMSOTf (587 μl, 721 mg, 3.24 mmol) was added to a stirred solution of (*N*,*N*-dibenzyl)aminoacetaldehyde diethyl acetal (339 mg, 1.018 mmol) in CH_2Cl_2 (7 ml) at −78 °C. The temperature was maintained at −78 °C for 30 min, then 1-cyclohexenyloxytrimethylsilane (757 μl, 662 mg, 3.89 mmol) was added. The mixture was stirred at −78 °C for a further 2 h, then ambient temperature for 3 h. A saturated solution of sodium hydrogen carbonate (20 ml) was added, and the product extracted with CH_2Cl_2 (3 × 25 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified by silica gel flash chromatography (eluent: petroleum ether/ethyl acetate/triethylamine 92 : 7 : 1) to yield (*E*)-2-(2-(*N*,*N*-dibenzylamino)-ethylidene)cyclohexanone as a colourless oil (192 mg, 6.01 μmol, 56%). δ_H (500 MHz, $CDCl_3$), 1.66–1.71 (2H, m, *cyclohexyl*–H4), 1.80–1.85 (2H, m, *cyclohexyl*–H5), 2.33–2.36 (2H, m, *cyclohexyl*–H3), 2.41 (2H, t, *J* 6.6, *cyclohexyl*–H6), 3.12 (2H, d, *J* 6.5, NCH_2CH), 3.59 (4H, s, $N(CH_2Ph)_2$), 6.78 (1H, tt, *J* 6.5, 2.1, NCH_2CH), 7.21–7.37 (10H, m, $N(CH_2Ph)_2$); δ_C (125 MHz, $CDCl_3$), 23.7 (*cyclohexyl*–C4), 23.9 (*cyclohexyl*–C5), 27.5 (*cyclohexyl*–C3), 40.6 (*cyclohexyl*–C6), 51.0 (NCH_2CH), 58.9 ($N(CH_2Ph)_2$), 127.4 (Ph), 128.6 (Ph), 129.2 (Ph), 136.9 (NCH_2CH), 138.2 (Ph), 139.6 (*cyclohexyl*–C2), 201.0 (*CO*); IR (liquid film), ν_{max}/cm^{-1} 1687, 1615, 1494, 1453, 1143, 1071, 1028, 739, 699; MS (FAB) *m/z* 320 (M$^+$1, 78%), 319 (M$^+$, 31%), 318 (40), 228 (18), 210 (21), 198 (5), 197 (21), 196 (25), 106 (24), 91 (100); Microanalysis: found C 82.45, H 7.9, N 4.35; calculated for $C_{22}H_{25}NO$: C 82.72, H 7.89, N 4.38. The *ketone* **19** (R = Bn) (52 mg, 14 μmol, 13%) was also isolated as a colourless oil with spectroscopic data identical to that reported above.

(*R*,*R*)-(−)-Bis(α-methylbenzyl)aminoacetaldehyde dimethyl acetal, 20. A solution of (*R*,*R*)-(−)-bis(α-methylbenzyl)amine (4.46 g, 19.8 mmol), sodium triacetoxyborohydride (6.29 g, 29.7 mmol), acetic acid (1.25 ml, 1.31 g, 21.8 mmol) and glyoxal 1,1-dimethyl acetal (45% solution in ^{t}butylmethyl ether, 13.8 g of solution, 59.4 mmol) was stirred at ambient temperature for 3 d. Sodium hydroxide solution (2 M, 100 ml) was added, and the product extracted with CH_2Cl_2 (3 × 100 ml), dried ($MgSO_4$) and concentrated *in vacuo*. ^{1}H NMR indicated an approximate 75 : 25 mixture of ((*R*,*R*)-(−)-bis(α-methylbenzylaminoacetaldehyde dimethyl acetal (**20**) and ((*R*,*R*)-(−)-bis(α-methylbenzylaminoacetic acid methyl ester (**21**). The product was dissolved in methanol (30 ml) and sodium hydroxide solution (2M, 5 ml), and heated at 50 °C for 16h. The solution was then concentrated *in vacuo*, water (10 ml) added, and the product extracted with diethyl ether (3 × 30 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified by silica gel flash chromatography (eluent petroleum ether/ethyl acetate/triethylamine 89.5 : 10 : 0.5) to yield *the acetal* (**20**) as a colourless oil (3.44 g, 11.0 mmol, 55%). $[\alpha]_D$ −41.7 ($CHCl_3$, *c* 1.2); δ_H (400 MHz, $CDCl_3$), 1.39 (6H, d, *J* 6.9, $N(CHCH_3Ph)_2$), 2.62 (1H, dd, *J* 14.7, 4.0, $NCH_2CH(OMe)_2$), 2.86 (1H, dd, *J* 14.7, 6.0, $NCH_2CH(OMe)_2$), 3.10 (3H, s, $CH(OCH_3)_2$), 3.33 (3H, s, $CH(OCH_3)_2$), 4.00 (2H, q, *J* 6.9, $N(CHCH_3Ph)_2$), 4.05 (1H, dd, *J* 5.9, 4.0, $NCH_2CH(OMe)_2$), 7.20–7.31 (10H, m, $N(CHCH_3Ph)_2$); δ_C (100 MHz, $CDCl_3$), 18.3 ($N(CHCH_3Ph)_2$), 48.6 ($NCH_2CH(OMe)_2$), 53.3 ($CH(OCH_3)_2$), 55.1 ($CH(OCH_3)_2$), 58.1 ($N(CHMePh)_2$), 106.4 ($CH(OCH_3)_2$), 126.5 (Ph), 127.9 (Ph), 144.8 (Ph); IR (liquid film), ν_{max} /cm^{-1} 2972, 2933, 2829, 1451, 1126, 1085, 700; HRMS (ES): 314.2113; calculated for $C_{20}H_{28}NO_2$: 314.2120; Microanalysis: found C 76.9, H 8.95, N 4.7; calculated for $C_{20}H_{27}NO_2$: C 76.64, H 8.68, N 4.47.

(*R*,*R*)-(−)-Bis(α-methylbenzyl)aminoacetaldehyde diethyl acetal, 23. A solution of (*R*,*R*)-(−)-bis(α-methylbenzyl) aminoacetaldehyde dimethyl acetal (**20**) (1.23 g, 3.92 mmol) and conc. sulfuric acid (1 ml) in ethanol (40 ml) was heated at 65 °C for 2 d. The solvent was removed *in vacuo*, sodium hydroxide solution (2 M, 100 ml) added, and the product extracted with diethyl ether (3 × 120 ml), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by silica gel flash chromatography (eluent: petroleum ether/ethyl acetate/triethylamine 92.5 : 7 : 0.5) gave *the acetal* (**23**) as a colourless oil (1.13g, 3.32 mmol, 85%). $[\alpha]_D$ −40.0 ($CHCl_3$, *c* 1.1); δ_H (400 MHz, $CDCl_3$), 1.09 (3H, t, *J* 7.0, OCH_2CH_3), 1.22 (3H, t, *J* 7.0, OCH_2CH_3), 1.39 (6H, d, *J* 6.9, $N(CHCH_3Ph)_2$), 2.62 (1H, dd, *J* 14.7, 3.8, $NCH_2CH(OEt)_2$), 2.92 (1H, dd, *J* 14.7, 6.2, $NCH_2CH(OEt)_2$), 3.31 (1H, dq, *J* 9.1, 7.0, $CH(OCH_2CH_3)_2$), 3.40 (1H, dq, *J* 9.1, 7.0, $CH(OCH_2CH_3)_2$), 3.52 (1H, dq, *J* 9.1, 7.0, $CH(OCH_2CH_3)_2$), 3.66 (1H, dq, *J* 9.1, 7.0, $CH(OCH_2CH_3)_2$), 3.98 (2H, q, *J* 6.9, $N(CHCH_3Ph)_2$), 4.22 (1H, dd, *J* 3.8, 6.2, $NCH_2CH(OEt)_2$), 7.18–7.32 (10H, m, $N(CHCH_3Ph)$); δ_C (100 MHz, $CDCl_3$), 15.7 (OCH_2CH_3), 15.9 (OCH_2CH_3), 19.1 ($N(CHCH_3Ph)_2$), 49.9 ($NCH_2CH(OEt)_2$), 58.6 ($N(CHMePh)_2$), 62.3 (OCH_2CH_3), 63.9 (OCH_2CH_3), 105.0 ($NCH_2CH(OEt)_2$), 126.9 (Ph), 128.3 (Ph), 145.3 (Ph); IR (neat), ν_{max}/cm^{-1} 2972, 2930, 2886, 1452, 1118, 1070, 700; MS (ES) *m/z* 342 (M$^+$1, 100%), 296 (20), 192 (10); HRMS (ES): 342.2431; calculated for $C_{22}H_{32}NO_2$: 342.2433; Microanalysis: found C 77.5, H 8.9, N 4.1; calculated for $C_{22}H_{31}NO_2$: C 77.38, H 9.15, N 4.10.

(*R*,*R*)-(−)-Bis(α-methylbenzyl)aminoacetaldehyde diisopropyl acetal, 24. A solution of (*R*,*R*)-(−)-bis(α-methylbenzyl)aminoacetaldehyde dimethyl acetal (**20**) (420 mg, 1.34 mmol), *p*-toluenesulfonic acid (765 mg, 4.02 mmol) and triisopropylorthoformate (4.36 ml, 5.10 g, 26.8 mmol) in 2-propanol (50 ml) was heated at 60 °C for 3 d. The solvent was removed *in vacuo*, then a saturated solution of sodium hydrogen carbonate (30 ml) was added added, and the product extracted with diethyl ether (3 × 40 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified by silica gel flash chromatography (eluent: petroleum ether/ethyl acetate/triethylamine 91.5 : 8 : 0.5) to yield *the acetal* (**24**) as a colourless oil (354 mg, 960 μmol, 72%). $[\alpha]_D$ −47.7 ($CHCl_3$, *c* 1.3); δ_H (500 MHz, $CDCl_3$), 1.01 (3H, d, *J* 6.1, OCH(CH_3)$_2$), 1.08 (3H, d, *J* 6.1, OCH(CH_3)$_2$), 1.20 (6H, d, *J* 6.1, OCH(CH_3)$_2$), 1.38 (6H, d, *J* 6.9, N(CH(CH_3)Ph)$_2$), 2.54 (1H, dd, *J* 14.8, 3.4, NCH_2CH(OPr^i)$_2$), 2.88 (1H, dd, *J* 14.8, 6.7, NCH_2CH(OPr^i)$_2$), 3.58 (1H, sept, *J* 6.1, OCH(CH$_3$)$_2$), 3.83 (1H, sept, *J* 6.1, OCH(CH$_3$)$_2$), 3.98 (2H, q, *J* 6.9, N(CH(CH$_3$)Ph)$_2$), 4.31 (1H, dd, *J* 6.7, 3.4, NCH$_2$CH(OPr^i)$_2$), 7.18–7.32 (10H, m, Ph); δ_C (125 MHz, $CDCl_3$), 19.5 (N(CH(*C*H$_3$)Ph)$_2$), 22.9 (OCH(*C*H$_3$)$_2$), 23.1 ((OCH(*C*H$_3$)$_2$), 23.5 ((OCH(*C*H$_3$)$_2$), 23.8 ((OCH(*C*H$_3$)$_2$), 51.2 (NCH_2CH(OPr^i)$_2$), 58.8 (N(CH(CH$_3$)Ph)$_2$), 68.6 ((O*C*H-(CH$_3$)$_2$), 69.2 ((O*C*H(CH$_3$)$_2$), 101.7 (NCH$_2$*C*H(OPr^i)$_2$), 126.8 (Ph), 128.3 (Ph), 128.4 (Ph), 145.4 (Ph); IR (neat), ν_{max} /cm^{-1} 1452, 1379, 1161, 1130, 1030, 760, 748, 700; MS (FAB) *m*/*z* 369 (M$^+$, 7%), 239 (10), 238 (59), 162 (10), 134 (13), 105 (100); Microanalysis: found C 77.75, H 9.75, N 3.65; calculated for $C_{24}H_{35}NO_2$: C 78.00, H 9.55, N 3.79.

((*R*,*R*)-(−)-Bis(α-methylbenzyl)amino)-2-methoxybutane, 25 (R = Me). Typical procedure A was used with TMSOTf (441 μl, 543 mg, 2.45 mmol), (*R*,*R*)-(−)-bis(α-methylbenzyl)aminoacetaldehyde dimethyl acetal (**20**) (255 mg, 814 μmol), and diethyl zinc (1.1 M solution in toluene, 1.61 ml, 1.79 mmol). The product was purified by silica gel flash chromatography (eluent: petroleum ether/ethyl acetate/triethylamine 96.5 : 3 : 0.5), to give *the ether* **25** (R = Me) as a colourless oil and an inseparable mixture of two diastereoisomers (170 mg, 547 μmol, 67%, dr 85 : 15 by ^{1}H NMR). Major diastereoisomer: δ_H (400 MHz, $CDCl_3$), 0.58 (3H, t, *J* 7.4, CH$_2$CH_3), 0.90–0.98 (1H, m, CH(OMe)CH_2CH$_3$), 1.25–1.33 (1H, m, CH(OMe)CH_2CH$_3$), 1.41 (6H, d, 6.8, N(CHCH_3Ph)$_2$), 2.33–2.39 (1H, m, NCH$_2$-CH(OMe)Et), 2.69–2.76 (2H, m, NCH_2CH(OMe)Et), 3.28 (3H, s, OCH_3), 3.99 (2H, q, *J* 6.8, N(CHCH$_3$Ph)$_2$), 7.19–7.30 (10H, m, N(CHCH$_3$*Ph*)$_2$); δ_C (100 MHz, $CDCl_3$), 9.2 (CH$_2$*C*H$_3$), 17.5 (N(CH*C*H$_3$Ph)$_2$), 24.4 (CH(OMe)*C*H$_2$CH$_3$), 49.8 (N*C*H$_2$CH(OMe)Et), 57.8 (*C*H(OMe)Et), 58.2 (O*C*H$_3$), 82.7 (N(*C*HCH$_3$Ph)$_2$), 126.5 (Ph), 127.9 (Ph), 128.1 (Ph), 144.8 (Ph); Mixture of diastereoisomers: $[\alpha]_D$ −16.9 ($CHCl_3$, *c* 1.3); IR (neat), ν_{max}/cm^{-1} 3026, 2969, 2930, 2874, 1494, 1453, 1117, 1088, 741, 698; HRMS (ES): 312.2335; calculated for $C_{21}H_{30}NO$: 312.2327; Microanalysis: found C 80.65, H 9.35, N 4.6; calculated for $C_{21}H_{29}NO$: C 80.78, H 9.36, N 4.49.

1-((*R*,*R*)-(−)-Bis(α-methylbenzyl)amino)-2-ethoxybutane, 25 (R = Et). Typical procedure A was used with TMSOTf (474 μl, 582 mg, 2.62 mmol), (*R*,*R*)-(−)-bis(α-methylbenzyl)aminoacetaldehyde diethyl acetal (298 mg, 876 μmol), and diethyl zinc (1.1 M solution in toluene, 1.57 ml, 216 mg, 1.75 mmol). The product was purified by silica gel flash chromatography (eluent: petroleum ether/ethyl acetate/triethylamine 95.5 : 4 : 0.5) to yield *the ether* **25** (R = Et) as a colourless oil and an inseparable mixture of two diastereoisomers (208 mg, 639 μmol, 73%, dr 85 : 15 by ^{1}H NMR). Major diastereoisomer: δ_H (300 MHz, $CDCl_3$), 0.61 (3H, t, *J* 7.3, CH(OEt)CH$_2$CH_3), 0.84–0.93 (1H, m, CH(OEt)CH_2CH$_3$), 1.13 (3H, t, *J* 6.9, CH(Et)OCH$_2$CH_3), 1.22–1.32 (1H, m, CH(OEt)CH_2CH$_3$), 1.40 (6H, d, *J* 6.9, N(CHCH_3Ph)$_2$), 2.34 (1H, dd, *J* 13.9, 6.3, NCH_2CH(OEt)Et), 2.72 (1H, dd, *J* 13.9, 5.8, NCH_2CH(OEt)Et), 2.77–2.83 (1H, m, NCH$_2$CH(OEt)Et), 3.36 (1H, dq, *J* 9.2, 6.9, CH(Et)OCH_2-CH$_3$), 3.52 (1H, dq, *J* 9.2, 6.9, CH(Et)OCH_2CH$_3$), 3.97 (2H, q, *J* 6.9, N(CHCH$_3$Ph)$_2$), 7.16–7.30 (10H, m, Ph); δ_C (75 MHz, $CDCl_3$), 9.9 (CH(OEt)CH$_2$*C*H$_3$), 16.1 (CH(Et)OCH$_2$*C*H$_3$), 18.1 (N(CH*C*H$_3$Ph)$_2$), 25.3 (CH(OEt)*C*H$_2$CH$_3$), 50.9 (N*C*H$_2$-CH(OEt)Et), 58.7 (*C*H(OEt)Et), 65.8 (CH(O*C*H$_2$CH$_3$)Et), 81.4 (N(*C*HCH$_3$Ph)$_2$), 127.0 (Ph), 128.3 (Ph), 128.5 (Ph), 145.3 (Ph); Mixture of diastereoisomers: $[\alpha]_D$ −12.3 ($CHCl_3$, *c* 1.3); MS (EI) *m*/*z* 325 (M$^+$, 4%), 239 (8), 238 (38), 134 (33), 105 (100); Microanalysis: found C 81.3, H 9.5, N 4.2; calculated for $C_{22}H_{31}NO$: C 81.18, H 9.60, N 4.30.

1-((*R*,*R*)-(−)-Bis(α-methylbenzyl)amino)-2-isopropoxybutane, 25 (R = Pr^i). Typical procedure A was used with TMSOTf (395 μl, 485 mg, 2.18 mmol), (*R*,*R*)-(−)-bis(α-methylbenzyl)-aminoacetaldehyde diisopropyl acetal (269 mg, 728 μmol), and diethyl zinc (1.1 M solution in toluene, 1.31 ml of solution, 180 mg, 1.45 mmol). The product was purified by silica gel flash chromatography (eluent: petroleum ether/ethyl acetate/triethylamine 96.5 : 3 : 0.5) to yield *the ether* **25** (R = Pr^i) as a colourless oil and an inseparable mixture of two diastereoisomers (178 mg, 523 μmol, 72%, dr 85 : 15 by ^{1}H NMR). Major diastereoisomer: δ_H (500 MHz, $CDCl_3$), 0.57 (3H, t, *J* 7.4, CH(OPr^i)CH$_2$CH_3), 0.67–0.76 (1H, m, CH(OPr^i)CH_2CH$_3$), 0.96 (3H, d, *J* 6.1, OCH(CH_3)$_2$), 1.08 (3H, d, *J* 6.1, OCH-(CH_3)$_2$), 1.26–1.32 (1H, m, CH(OPr^i)CH_2CH$_3$), 1.41 (6H, d, *J* 6.8, N(CHCH_3Ph)$_2$), 2.33 (1H, dd, *J* 13.9, 7.7, NCH_2CH-(OPr^i)Et), 2.62 (1H, dd, *J* 13.9, 5.1, NCH_2CH(OPr^i)Et), 2.76–2.81 (1H, m, CH(OPr^i)Et), 3.47 (1H, hept, *J* 6.1, OCH(CH$_3$)$_2$), 3.98 (2H, q, *J* 6.8, N(CHCH$_3$Ph)$_2$), 7.17–7.30 (10H, m, Ph); δ_C (75 MHz, $CDCl_3$), 9.6 (CH(OPr^i)CH$_2$*C*H$_3$), 17.3 (N(CH-*C*H$_3$Ph)$_2$), 22.5 (OCH(*C*H$_3$)$_2$), 23.0 (OCH(*C*H$_3$)$_2$), 25.2 (CH(OPr^i)*C*H$_2$CH$_3$), 51.3 (N*C*H$_2$CH), 58.3 (*C*H(OPr^i)Et), 69.9 (O*C*H(CH$_3$)$_2$), 77.6 (N(*C*HCH$_3$Ph)$_2$), 126.5 (Ph), 127.8 (Ph), 128.1 (Ph), 144.9 (Ph); $[\alpha]_D$ −16.0 ($CHCl_3$, *c* 1.0); Mixture of diastereoisomers: IR (neat), ν_{max}/cm^{-1} 2970, 1452, 1377, 1265, 741, 700; MS (EI) *m*/*z* 339 (M$^+$, 0.4%), 239 (7), 238 (37), 134 (24), 105 (100); Microanalysis: found C 81.2, H 9.6, N 3.95; calculated for $C_{23}H_{33}NO$: C 81.37, H 9.80, N 4.13.

((*R*,*R*)-(−)-Bis(α-methylbenzyl)amino)-2-methoxy-3-methylbutane, 26 (R = Me). TMSOTf (612 μl, 751 mg, 3.38 mmol) was added to a stirred solution of (*R*,*R*)-(−)-bis(α-methylbenzyl)-aminoacetaldehyde dimethyl acetal (353 mg, 1.13 mmol) in CH_2Cl_2 (7 ml) at −78 °C. The temperature was maintained at −78 °C for 30 min. A solution of zinc chloride (45% solution in CH_2Cl_2, 439 μl, 261 mg, 1.23 mmol) was added to isopropyl magnesium chloride (2.0 M solution in diethyl ether, 1.24 ml, 2.48 mmol), in CH_2Cl_2 (3 ml) at −78 °C and after 10 min was allowed to warm to rt and stirred for 30 min. The solution of organozinc reagent was re-cooled to −78 °C then added by cannula to the above reaction mixture. The mixture was stirred at −78 °C for a further 3 h, then allowed to warm to rt. After 14 h, a saturated solution of sodium hydrogen carbonate (20 ml) was added, the product extracted with CH_2Cl_2 (3 × 25 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified by silica gel flash chromatography (eluent: petroleum ether/ethyl acetate/triethylamine 95.5 : 4 : 0.5), to give *the ether* **26** (R = Me) as a colourless oil and an inseparable mixture of two diastereoisomers (129 mg, 396 μmol, 53%, dr 55 : 45 by ^{1}H NMR). Major diastereoisomer: δ_H (500 MHz, $CDCl_3$), 0.45 (3H, d, *J* 6.8, CH(CH_3)CH_3), 0.77 (3H, d, *J* 5.2, CH(CH_3)CH$_3$), 1.41 (6H, d, *J* 6.8, N(CHCH_3Ph)$_2$), 1.60–1.64 (1H, m, CH(CH$_3$)-CH$_3$), 2.38–2.43 (1H, m, NCH$_2$CH(OMe)), 2.70–2.75 (2H, m, NCH_2CH(OMe)), 3.38 (3H, s, OCH_3), 3.98 (2H, q, *J* 6.8, N(CHCH$_3$Ph)$_2$), 7.15–7.34 (10H, m, Ph); δ_C (125 MHz, $CDCl_3$), 16.0 (CH(CH$_3$)*C*H$_3$), 18.1 (N(CH*C*H$_3$Ph)$_2$), 19.4 (CH(*C*H$_3$)CH$_3$), 29.6 (*C*H(CH$_3$)CH$_3$), 48.0 (NCH_2CH(OMe)), 58.4 (O*C*H$_3$), 59.3 (NCH$_2$*C*H(OCH$_3$)), 86.5 (N(*C*HCH$_3$Ph)$_2$),

126.5 (Ph), 127.9 (Ph), 128.1 (Ph), 145.0 (Ph); Minor diastereoisomer: δ_H (500 MHz, $CDCl_3$), 0.76 (6H, d, *J* 5.6, C*H*(CH_3)CH_3), 1.41 (6H, d, *J* 6.8, N(CHCH_3Ph)$_2$), 1.83–1.90 (1H, m, C*H*(CH_3)CH_3), 2.59 (1H, dd, *J* 14.2, 5.7, NCH_2CH(OMe)), 2.73–2.76 (1H, m, NCH_2CH(OMe)), 2.78–2.81 (1H, m, NCH_2-C*H*(OMe)), 3.25 (3H, s, OCH_3), 3.95 (2H, q, *J* 6.8, N(C*H*-CH_3Ph)$_2$), 7.15–7.34 (10H, m, Ph); δ_C (125 MHz, $CDCl_3$), 16.3 (CH(CH_3)*C*H_3), 18.2 (N(CH*C*H_3Ph)$_2$), 19.8 (CH(*C*H_3)CH_3), 29.3 (*C*H(CH_3)CH_3), 47.1 (NCH_2CH(OMe)), 58.4 (O*C*H_3), 58.8 (NCH_2*C*H(OCH_3)), 85.8 (N(*C*HCH_3Ph)$_2$), 126.4 (Ph), 127.9 (Ph), 128.2 (Ph), 145.0 (Ph); Mixture of diastereoisomers: $[\alpha]_D$ −26.7 ($CHCl_3$, *c* 0.3); IR (neat), ν_{max}/cm^{-1} 2966, 2928, 2874, 1492, 1451, 1370, 1154, 1094, 1060, 1028, 760, 750, 700; MS (FAB) *m*/*z* 326 (M^+, 14%), 324 (8), 239 (16), 238 (87), 134 (20), 105 (100); Microanalysis: found C 80.95, H 9.65, N 4.1; calculated for $C_{22}H_{31}NO$: C 81.18, H 9.60, N 4.30.

((*R*,*R*)-(−)-Bis(α-methylbenzyl)amino)-2-methoxybutane, 27 (R = Me). ^{n}Butyllithium (1.6M solution in hexanes, 1.7 ml, 270 mmol) was added to a solution of copper(I) iodide (257 mg, 1.35 mmol) in THF (5 ml), and the mixture was stirred at 0 °C for 45 min. TMSOTf (489 µl, 600 mg, 2.70 mmol) was added to a stirred solution of (*R,R*)-(−)-bis(α-methylbenzyl)amino-acetaldehyde dimethyl acetal (282 mg, 900 µmol) in CH_2Cl_2 (7 ml) at −78 °C. After 30 min the solution of organocuprate reagent was added *via* cannula. The mixture was stirred at −78 °C for a further 3 h, then allowed to warm to rt. After 18h, a saturated solution of sodium hydrogen carbonate (20 ml) was added, the product extracted with CH_2Cl_2 (3 × 25 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified by silica gel flash chromatography (eluent: petroleum ether/ethyl acetate/triethylamine 96 : 3 : 1), to give *the ether* **27** (R = Me) as a colourless oil and an inseparable mixture of two diastereoisomers (220 mg, 648 µmol, 72%, dr 62 : 38 by ^{1}H NMR). Major diastereoisomer: δ_H (500 MHz, $CDCl_3$), 0.89 (3H, t, *J* 7.2, CH_2CH_3), 1.07–1.17 (2H, m, C$H_2$$CH_3$), 1.22–1.30 (3H, m, C$H_2CH_2$$CH_2$$CH_3$), 1.34 (6H, d, 6.9, N(CHCH_3Ph)$_2$), 1.64–1.71 (1H, m, C$H_2$$CH_2$$CH_2$$CH_3$), 2.59 (1H, dd, *J* 14.2, 5.0, NCH_2CH(OMe)Bu), 2.67 (1H, dd, *J* 14.2, 7.4, NCH_2-CH(OMe)Bu), 2.96–3.00 (1H, m, NCH$_2$C*H*(OMe)Bu), 3.24 (3H, s, OCH_3), 3.93 (2H, q, *J* 6.9, N(C*H*CH_3Ph)$_2$), 7.19–7.30 (10H, m, N(CHCH_3*Ph*)$_2$); δ_C (125 MHz, $CDCl_3$), 14.1 (CH_2-*C*H_3), 19.2 (N(CH*C*H_3Ph)$_2$), 22.9 ($CH_2$$CH_2$*C*$H_2$$CH_3$), 27.9 ($CH_2$*C*$H_2$$CH_2$$CH_3$), 32.5 (*C*$H_2$$CH_2$$CH_2$$CH_3$), 49.2 (N*C*$H_2$-CH(OMe)Bu), 57.4 (NCH$_2$*C*H(OMe)Bu), 58.9 (O*C*$H_3$), 82.7 (N(*C*HC$H_3$Ph)$_2$), 126.6 (Ph), 127.9 (Ph), 128.0 (Ph), 144.8 (Ph); Mixture of diastereoisomers: $[\alpha]_D$ −66.7 ($CHCl_3$, *c* 1.2); IR (neat), ν_{max}/cm^{-1} 2967, 2931, 1493, 1452, 1094, 760, 740, 701; MS (ES) *m*/*z* 341 (M + 2, 38%), 340 (M + 1, 100%), 236 (90); Microanalysis: found C 81.2, H 9.95, N 4.1; calculated for $C_{23}H_{33}NO$: C 81.37, H 9.80, N 4.13.

1-[(*R*,*R*)-(−)-Bis(α-methylbenzylamino)methoxyethyl]-1*H*-pyrimidine-2,4-dione, 28 (R = Me). Typical procedure B was used with TMSOTf (288 µl, 353 mg, 1.59 mmol), (*R*,*R*)-(−)-bis(α-methylbenzyl)aminoacetaldehyde dimethyl acetal (166 mg, 530 µmol), and bis(*O*-trimethylsilyl)uracil (272 mg, 1.06 mmol). The product was purified by silica gel flash chromatography (eluent: gradient of petroleum ether/ethyl acetate/triethylamine 69 : 30 : 1–49 : 50 : 1), to give *the uracil derivative* **28** (R = Me) as an amorphous colourless solid and an inseparable mixture of two diastereoisomers (178 mg, 452 µmol, 85%, dr 55 : 45 by ^{1}H NMR). Major diastereoisomer: δ_H (300 MHz, $CDCl_3$), 1.45 (6H, d, *J* 6.9, N(CHCH_3Ph)$_2$), 2.72 (1H, dd, *J* 14.5, 8.0, NCH_2CH), 2.96 (1H, dd, *J* 14.5, 4.2, NCH_2CH), 3.08 (3H, s, OCH_3), 4.05 (2H, q, *J* 6.9, N(C*H*CH_3Ph)$_2$), 5.23 (1H, d, *J* 8.1, *uracil*–C*H*), 5.35–5.38 (1H, m, NCH$_2$C*H*-(N)OMe), 6.51 (1H, d, *J* 8.1, *uracil*–C*H*), 7.19–7.33 (10H, m, Ar); δ_C (75 MHz, $CDCl_3$), 16.1 (N(CH*C*H_3Ph)$_2$), 49.1 (NCH_2CH), 56.8 (OCH_3), 57.5 (N(*C*HCH$_3$Ph)$_2$), 85.6 (*uracil*–*C*H), 102.9 (NCH$_2$*C*H(N)OMe), 127.4 (Ph), 128.2 (Ph), 128.6 (Ph), 138.6 (*uracil*–*C*H), 143.9 (Ph), 151.6 (*uracil*–*C*O), 163.6 (*uracil*–*C*O). Minor diastereoisomer: δ_H (300 MHz, $CDCl_3$), 1.35 (6H, d, *J* 6.9, N(CHCH_3Ph)$_2$), 2.76 (1H, dd, *J* 15.1, 4.4, NCH_2CH), 2.94 (1H, dd, *J* 15.1, 6.6, NCH_2CH), 3.17 (3H, s, OCH_3), 3.97 (2H, q, *J* 6.9, N(C*H*CH$_3$Ph)$_2$), 5.63 (1H, d, *J* 8.1, *uracil*–C*H*), 5.32–5.35 (1H, m, NCH$_2$C*H*(N)OMe), 7.13 (1H, d, *J* 8.1, *uracil*–C*H*), 7.19–7.33 (10H, m, Ar); δ_C (75 MHz, $CDCl_3$), 19.8 (N(CH*C*H_3Ph)$_2$), 50.4 (NCH_2CH), 57.1 (OCH_3), 59.4 (N(*C*HCH$_3$Ph)$_2$), 88.1 (*uracil*–*C*H), 102.9 (NCH$_2$*C*H-(N)OMe), 127.4 (Ph), 128.2 (Ph), 128.6 (Ph), 139.7 (*uracil*–*C*H), 144.2 (Ph), 151.4 (*uracil*–*C*O), 163.5 (*uracil*–*C*O). Mixture of diastereoisomers: mp 50–52 °C; $[\alpha]_D$ +23.3 ($CHCl_3$, *c* 1.2); IR (neat), ν_{max}/cm^{-1} 1758, 1261, 1091, 723, 702; MS (EI) *m*/*z* 281 (5%), 239 (6), 238 (31), 105 (100).

1-[(*R*,*R*)-(−)-Bis(α-methylbenzylamino)isopropoxy-ethyl]-1*H*-pyrimidine-2,4-dione, 28 (R = Pr^i). Typical procedure B was used with TMSOTf (395 µl, 485 mg, 2.18 mmol), (*R*,*R*)-(−)-bis(α-methylbenzyl)aminoacetaldehyde dimethyl acetal (269 mg, 728 µmol), and bis(*O*-trimethylsilyl)uracil (373 mg, 1.46 mmol). The product was purified by silica gel flash chromatography (eluent: gradient of petroleum ether/ethyl acetate/triethylamine 69 : 30 : 1–49 : 50 : 1), to yield *the uracil derivative* **28** (R = Pr^i) as an amorphous colourless solid and an inseparable mixture of two diastereoisomers (234 mg, 555 µmol, 76%, dr 55 : 45 by ^{1}H NMR). Major diastereoisomer: δ_H (500 MHz, $CDCl_3$), 0.97 (3H, d, *J* 6.1, OCH(CH_3)$_2$), 1.01 (3H, d, *J* 6.1, OCH(CH_3)$_2$), 1.45 (6H, d, *J* 6.8, N(CHCH_3Ph)$_2$), 2.68 (1H, dd, *J* 14.6, 7.9, NCH_2CH), 2.89 (1H, dd, *J* 14.6, 4.4, NCH_2CH), 3.41 (1H, hept, *J* 6.1, OC*H*(CH_3)$_2$), 4.04 (2H, q, *J* 6.8, N(C*H*-CH_3Ph)$_2$), 5.22 (1H, d, *J* 8.1, *uracil*–C*H*), 5.57 (1H, dd, *J* 7.8, 4.4, NCH$_2$C*H*(N)OPr^i), 6.63 (1H, d, *J* 8.1, *uracil*–C*H*), 7.19–7.32 (10H, m, Ar), 9.30 (1H, s, br, N*H*); δ_C (125 MHz, $CDCl_3$), 16.4 (N(CH*C*H_3Ph)$_2$), 21.3 (OCH(*C*H_3)$_2$), 21.4 (OCH(*C*H_3)$_2$), 49.5 (NCH_2CH), 57.6 (N(*C*HCH$_3$Ph)$_2$), 70.6 (O*C*H(CH_3)$_2$), 81.6 (*uracil*–*C*H), 102.3 (NCH$_2$*C*H(N)OPr^i), 127.0 (Ph), 128.2 (Ph), 128.3 (Ph), 138.5 (*uracil*–*C*H), 143.5 (Ph), 151.2 (*uracil*–*C*O), 163.5 (*uracil*–*C*O). Minor diastereoisomer: δ_H (500 MHz, $CDCl_3$), 1.08 (3H, d, *J* 6.2, OCH(CH_3)$_2$), 1.14 (3H, d, *J* 6.1, OCH(CH_3)$_2$), 1.34 (6H, d, *J* 6.9, N(CHCH_3Ph)$_2$), 2.71 (1H, dd, *J* 15.1, 4.3, NCH_2CH), 2.97 (1H, dd, *J* 15.1, 7.0, NCH_2CH), 3.57 (1H, hept, *J* 6.1, OC*H*(CH_3)$_2$), 3.92 (2H, q, *J* 6.9, N(C*H*-CH_3Ph)$_2$), 5.68 (1H, d, *J* 8.1, *uracil*–C*H*), 5.69–5.73 (1H, m, NCH$_2$C*H*(N)OPr^i), 7.20 (1H, d, *J* 8.1, *uracil*–C*H*), 7.19–7.32 (10H, m, Ar), 9.25 (1H, s, br, N*H*); δ_C (125 MHz, $CDCl_3$), 20.0 (N(CH*C*H_3Ph)$_2$), 22.7 (OCH(*C*H_3)$_2$), 22.8 (OCH(*C*H_3)$_2$), 50.4 (NCH_2CH), 59.1 (N(*C*HCH$_3$Ph)$_2$), 70.8 (O*C*H(CH_3)$_2$), 83.7 (*uracil*–*C*H), 102.3 (NCH$_2$*C*H(N)OPr^i), 126.9 (Ph), 127.8 (Ph), 128.3 (Ph), 138.8 (*uracil*–*C*H), 143.7 (Ph), 151.1 (*uracil*–*C*O), 163.6 (*uracil*–*C*O). Mixture of diastereoisomers: mp 50–52 °C; $[\alpha]_D$ −16.7 ($CHCl_3$, *c* 1.2); IR (neat), ν_{max}/cm^{-1} 3060, 3029, 2975, 2935, 2873, 1717, 1463, 1071, 919, 762, 727, 701, 648; MS (EI) *m*/*z* 422 (M^+, 0.4%), 239 (37), 238 (86), 141 (17), 134 (64), 106 (38), 105 (100); HRMS (ES): 444.2255; calculated for $C_{25}H_{31}N_3O_3Na$: 444.2263.

1-[(*R*,*R*)-(−)-Bis(α-methylbenzylamino)-methoxyethyl]-1*H*-pyridine-2-one, 29 (R = Me). Typical procedure B was used with TMSOTf (471 µl, 579 mg, 2.60 mmol), *(R,R)-(−)*-bis(α-methylbenzyl)aminoacetaldehyde dimethyl acetal (272 mg, 868 µmol), and 2-trimethylsilyloxypyridine (0.3 ml, 290 mg, 1.74 mmol). The product was purified by silica gel flash chromatography (eluent: petroleum ether/ethyl acetate/triethylamine 69 : 30 : 1), to give *the pyridone* **29** (R = Me) as a colourless amorphous solid and an inseparable mixture of two diastereoisomers (268 mg, 713 µmol, 82%, dr 70 : 30 by ^{1}H NMR). Major diastereoisomer: δ_H (400 MHz, $CDCl_3$), 1.45 (6H, d, *J* 6.9, N(CHCH_3Ph)$_2$), 2.76 (1H, dd, *J* 14.2, 6.2, NCH_2CH-(py)OMe), 3.04 (1H, dd, *J* 14.2, 6.5, NCH_2CH(py)OMe), 3.17

(3H, s, OCH_3), 4.03 (2H, q, *J* 6.9, N(CHCH$_3$Ph)$_2$), 5.94 (1H, t, *J* 6.2, NCH$_2$CH(py)OMe), 5.97 (1H, t, *J* 6.6, *py*5–CH), 6.50 (1H, d, *J* 9.1, *py*3–CH), 6.97, (1H, d, *J* 6.9, *py*4–CH), 7.16–7.19 (1H, m, *py*6–CH), 7.19–7.35 (10H, m, Ar); δ_C (100 MHz, CDCl$_3$), 18.0 (N(CHCH$_3$Ph)$_2$), 49.9 (NCH$_2$CH(py)OMe), 58.0 (OCH$_3$), 59.1 (N(CHCH$_3$Ph)$_2$), 85.9 (NCH$_2$$C$H(N)OMe), 106.4 (*py*5–$C$H), 120.9 (*py*3–$C$H), 127.0 (Ph), 128.1 (Ph), 128.3 (Ph), 132.4 (*py*4–CH), 139.5 (*py*6–CH), 144.7 (Ph), 163.4 (*py*2–CO). Minor diastereoisomer: δ_H (400 MHz, CDCl$_3$), 1.35 (6H, d, *J* 6.9, N(CHCH_3Ph)$_2$), 2.74 (1H, dd, *J* 14.2, 6.2, NCH_2CH(N)OMe), 3.01 (1H, dd, *J* 14.2, 6.5, NCH_2CH(N)OMe), 3.23 (3H, s, OCH_3), 3.96 (2H, q, *J* 6.9, N(CHCH$_3$Ph)$_2$), 5.94 (1H, t, *J* 6.2, NCH$_2$CH(N)OMe), 6.18 (1H, t, *J* 6.7, *py*5–CH), 6.56 (1H, d, *J* 9.1, *py*3–CH), 7.33, (1H, d, *J* 7.2, *py*4–CH), 7.15–7.17 (1H, m, *py*6–CH), 7.19–7.35 (10H, m, Ar). δ_C (100 MHz, CDCl$_3$), 20.2 (N(CHCH$_3$Ph)$_2$), 51.0 (NCH$_2$CH(py)OMe), 57.2 (OCH$_3$), 59.1 (N(CHCH$_3$Ph)$_2$), 85.9 (NCH$_2$$C$H(N)OMe), 106.4 (*py*5–$C$H), 121.3 (*py*3–$C$H), 127.0 (Ph), 128.1 (Ph), 128.3 (Ph), 132.5 (py4–CH), 139.5 (*py*6–CH), 144.8 (Ph), 163.4 (*py*2–CO). Mixture of diastereoisomers: mp 107–110 °C; $[\alpha]_D$ –45.5 (CHCl$_3$, *c* 1.1); IR (neat), ν_{max}/cm^{-1} 2921, 2853, 1660, 1588, 1538, 1461, 1377; HRMS (ES): 377.2212; calculated for $C_{24}H_{29}N_2O_2$: 377.2229; Microanalysis: found C 76.6, H 7.5, N 7.5; calculated for $C_{24}H_{28}N_2O_2$: C 76.56, H 7.50, N 7.44.

2-[2-(*R*,*R*)-(−)-Bis(α-methylbenzylamino)-1-methoxyethyl]-cyclohexanone, 30 (R = Me). Typical procedure C was used with TMSOTf (612 µl, 751 mg, 3.38 mmol), ((*R*,*R*)-(−)-bis(α-methylbenzyl)aminoacetaldehyde dimethyl acetal (353 mg, 1.13 mmol), and 1-morpholinocyclohexene (283 mg, 1.70 mmol). The product was purified by silica gel flash chromatography (eluent: petroleum ether/ethyl acetate/triethylamine 89.5 : 10 : 0.5), to give *the ketone* (**30**) R = Me as a colourless liquid (299 mg, 818 µmol, 86%) and a 13 : 6 : 4 : 2 mixture of diastereoisomers. Major diastereoisomer: δ_H (500 MHz, CDCl$_3$), 0.96–0.99 (1H, m, *cyclohexyl*-H5$_{ax}$), 1.46 (6H, d, *J* 6.9, N(CH-(CH_3)Ph)$_2$), 1.53–1.58 (1H, m, *cyclohexyl*-H6$_{ax}$), 1.81–1.88 (1H, m, *cyclohexyl*-H5$_{eq}$), 1.91–1.97 (1H, m, *cyclohexyl*-H4$_{ax}$), 2.02–2.08 (1H, m, *cyclohexyl*-H6$_{eq}$), 2.11–2.16 (1H, m, *cyclohexyl*-H4$_{eq}$), 2.27–2.31 (1H, m, *cyclohexyl*-H3$_{ax}$), 2.30–2.35 (1H, m, *cyclohexyl*-H3$_{eq}$), 2.53 (1H, dd, *J* 14.1, 4.9, NCH_2CH(OMe)), 2.73 (1H, dd, *J* 14.1, 8.5, NCH_2CH(OMe)), 2.59–2.63 (1H, m, *cyclohexyl*-H2$_{ax}$), 3.73–3.76 (1H, m, NCH$_2$CH(OMe)), 3.25 (3H, s, OCH_3), 4.02 (2H, q, *J* 6.9, N(CHMePh)$_2$), 7.18–7.30 (10H, m, N(CHMe*Ph*)$_2$); Mixture of diastereoisomers: IR (neat), ν_{max}/cm^{-1} 1708, 1450, 1101, 761(s), 752, 701; MS (FAB) *m*/*z* 379 (M$^+$, 31%), 378 (35), 302 (14), 238 (30), 105 (100).

[2,2-Bis-(1*H*-indol-3-yl)ethyl]-[(*R*,*R*)-(−)-bis(α-methylbenzylamine] 31. TMSOTf (409 µl, 502 mg, 2.26 mmol) was added to a stirred solution of (*R*,*R*)-(−)-bis(α-methylbenzyl)-aminoacetaldehyde dimethyl acetal (236 mg, 753 µmol) in CH$_2$Cl$_2$ (7 ml) at −78 °C. The temperature was maintained at −78 °C for 30 min, then indole (441 mg, 3.77 mmol) added. The mixture was stirred at −78 °C for a further 3h, then allowed to warm to rt. After 14 h, a saturated solution of sodium hydrogen carbonate (20 ml) was added, the product extracted with CH$_2$Cl$_2$ (3 × 25 ml), dried (Na$_2$SO$_4$) and concentrated *in vacuo*. The product was purified by silica gel flash chromatography (eluent: gradient of petroleum ether/ethyl acetate/triethylamine 79 : 20 : 1–69 : 30 : 1 to ethyl acetate), to give *the bis-indole* **31** as colourless plates (234 mg, 483 µmol, 64%). M.p. 78–81 °C; δ_H (300 MHz, CDCl$_3$), 1.37 (6H, d, *J* 6.9, N(CHCH_3Ph)$_2$), 3.21 (1H, dd, *J* 13.4, 8.3, NCH_2CH), 3.51 (1H, dd, *J* 13.4, 6.3, NCH_2CH), 4.07 (2H, q, *J* 6.9, N(CHCH$_3$Ph)$_2$), 4.62–4.68 (1H, m, NCH$_2$CH), 6.40 (1H, d, *J* 2.2, *indole*-C2H), 6.76 (1H, d, *J* 2.3, *indole*-C2H), 7.05–7.35 (18H, m, Ar), 7.68 (1H, s, *indole*-NH), 7.78 (1H, s, *indole*-NH); δ_C (75 MHz, CDCl$_3$), 16.5 (N(CHCH$_3$Ph)$_2$), 34.2 (NCH$_2$$C$H), 51.0 (N$CH_2$CH), 56.6 (N($CHCH_3$Ph)$_2$), 111.1 (*indole*-*C*2), 111.6 (*indole*-*C*2), 118.2 (Ar), 119.2 (Ar), 119.5 (Ar), 120.0 (Ar), 120.1 (Ar), 121.8 (Ar), 122.1 (Ar), 122.4 (Ar), 122.8 (Ar), 126.7 (Ar), 127.6 (Ar), 127.9 (Ar), 128.1 (Ar), 128.7 (Ar), 136.6 (Ar), 136.9 (Ar), 145.2 (Ar), 145.3(Ar); IR (neat), ν_{max}/cm^{-1} 3418, 1455, 740, 701; MS (ES) *m*/*z* 485 (M + 2, 12%), 484 (M + 1, 100%).

3-(2-Indolyl)indole (174 mg, 744 µmol) was also isolated.[29] δ_H (300 MHz, CDCl$_3$), 3.21 (1H, dd, *J* 15.6, 8.3, NCHCH_2), 3.48 (1H, dd, *J* 15.6, 9.1, NCHCH_2), 5.26 (1H, t, *J* 8.6, NCHCH$_2$), 6.67 (1H, d, *J* 7.7, *indole*C2H), 6.75 (1H, t, *J* 7.4, Ar), 7.05–7.25 (5H, m, Ar), 7.36 (1H, d, *J* 8.1, Ar), 7.59 (1H, dd, *J* 7.9, 0.5, Ar), 7.99 (1H, s, br, NH); δ_C (75 MHz, CDCl$_3$), 38.1 (NCHCH$_2$), 56.8 (NCHCH$_2$), 109.6 (Ar), 111.7 (Ar), 119.2 (Ar), 119.8 (Ar), 119.9 (Ar), 120.0 (Ar), 121.6 (Ar), 122.7 (Ar), 125.1 (Ar), 126.2 (Ar), 127.9 (Ar), 129.3 (Ar), 137.1 (Ar), 151.3 (Ar); IR (neat), ν_{max}/cm^{-1} 3413, 1607, 1484, 1463, 1422, 1245, 1229, 1152 (m), 1096, 1034, 1011, 905, 742, 701; MS (ES) *m*/*z* 236 (M + 2, 11%), 235 (M + 1, 100%).

4-Methoxy-1*R*-methyl-2-((*R*)-α-methylbenzyl)-1,2,3,4-tetrahydroisoquinoline, 32 (R = Me). TMSOTf (728 µl, 893 mg, 4.02 mmol) was added to a stirred solution of (*R,R*)-(−)-bis(α-methylbenzyl)aminoacetaldehyde dimethyl acetal (252 mg, 804 µmol) in CH$_2$Cl$_2$ (7 ml) at −78 °C. The mixture was stirred at −78 °C for 3 h then rt for 3 d. After 14 h, a saturated solution of sodium hydrogen carbonate (20 ml) was added, the product extracted with CH$_2$Cl$_2$ (3 × 25 ml), dried (Na$_2$SO$_4$) and concentrated. The product was purified by silica gel flash chromatography (eluent: petroleum ether/ethyl acetate/triethylamine 92.5 : 7 : 0.5), to give *the tetrahydroisoquinoline* **32** (R = Me) as a colourless oil and an inseparable mixture of two diastereoisomers (156 mg, 556 µmol, 69%, dr 90 : 10 by ^{1}H NMR). Major diastereoisomer: δ_H (500 MHz, CDCl$_3$), 1.29 (3H, d, *J* 6.7, NCH(CH_3)Ph), 1.44 (3H, d, *J* 6.5, NCH(CH_3)Ar), 2.77 (1H, dd, *J* 13.5, 3.1, NCH_2CHOMe), 2.96 (1H, dd, *J* 13.5, 2.1, NCH_2CHOMe), 3.20 (3H, s, OCH_3), 3.82 (1H, q, *J* 6.5, NCH-(CH$_3$)Ar), 4.02 (1H, t, *J* 2.8, NCH$_2$CHOMe), 4.37 (1H, q, *J* 6.7, NCH(CH$_3$)Ph), 7.08–7.46 (9H, m, Ar). δ_C (125 MHz, CDCl$_3$), 15.4 (NCH(CH$_3$)Ph), 20.6 (NCH(CH$_3$)Ar), 43.0 (NCH$_2$-CHOMe), 53.1 (OCH$_3$), 56.6 (NCH(CH$_3$)Ar), 60.1 (NCH-(CH$_3$)Ph), 75.7 (NCH$_2$$C$HOMe), 126.3 (Ar), 126.8 (Ar), 127.1 (Ar), 127.6 (Ar), 127.7 (Ar), 128.3 (Ar), 129.8 (Ar), 134.0 (Ar), 141.4 (Ar), 146.2 (Ar); Mixture of diastereoisomers: $[\alpha]_D$ −46.2 (CHCl$_3$, *c* 1.3); IR (neat), ν_{max}/cm^{-1} 1491, 1452, 1087, 1060, 757, 701; MS (FAB) *m*/*z* 282 (M$^+$1, 41%), 239 (M$^+$, 23%), 280 (56), 267 (21), 266 (100), 250 (20), 146 (25), 105 (88); Microanalysis: found C 80.8, H 8.35, N 4.9; calculated for $C_{19}H_{23}NO$: C 81.10, H 8.24, N 4.98.

Typical procedure D

(*S*)-2-(*N*,*N*-Dibenzyl)amino-3-phenylpropanal diethyl acetal, 35 (R = Bn).[30] A solution of dimethyl sulfoxide (3.20 ml, 3.52g, 45.1 mmol) in CH$_2$Cl$_2$ (10 ml) was added dropwise over 3 min to a stirred solution of oxalyl chloride (1.97 ml, 2.86g, 22.6 mmol) in CH$_2$Cl$_2$ (50 ml) at −61°C (cardice/chloroform bath). After 5 min of stirring, a solution of-2-(*N*,*N*-dibenzylamino)-3-phenyl-1-propanol (6.80g, 20.5 mmol) in CH$_2$Cl$_2$ (25 ml) was added dropwise over 5 min. After a further 30 min, triethylamine (14.3 ml, 10.4g, 103 mmol) was added, and the mixture stirred for 1 h at −61 °C, then 2 h at ambient temperature. Water (120 ml) was added, and the aqueous layer extracted with CH$_2$Cl$_2$ (3 × 100 ml). Combined organic extracts were dried (Na$_2$SO$_4$) and concentrated *in vacuo*, to yield-2-(*N*,*N*-dibenzylamino)-3-phenylpropanal **34** (R = Bn) (6.15g, 18.7 mmol, 91%). The crude aldehyde was added to a solution of triethyl orthoformate (34.1 ml, 30.4g, 205 mmol), HCl (1.0M solution in diethyl ether, 45.1 ml, 45.1 mmol) and concentrated sulfuric acid (0.5 ml) in ethanol (100 ml). The solution was stirred at ambient temperature for 2 d. A saturated solution of sodium hydrogen carbonate (150 ml) was added and the product

extracted with diethyl ether (3 × 150 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified by silica gel flash chromatography chromatography (eluent: petroleum ether/ethyl acetate/triethylamine 89.5 : 10 : 0.5) to give the acetal[30] **35** (R = Bn) (7.11g, 17.6 mmol, 94%) as a colourless oil. $[\alpha]_D$ −17.8 ($CHCl_3$, *c* 0.9); δ_H (400 MHz, $CDCl_3$), 1.20 (6H, t, *J* 7.1, OCH_2CH_3), 2.88 (1H, dd, *J* 14.2, 9.3, NCH(CH_2Ph)), 2.93 (1H, dd, *J* 14.2, 4.7, NCH(CH_2Ph)), 3.10 (1H, quin, *J* 4.6, NC*H*(CH_2Ph), 3.37 (1H, dq, *J* 9.2, 7.1, CH(OCH_2CH_3)$_2$), 3.50 (1H, dq, *J* 9.2, 7.1, CH(OCH_2CH_3)$_2$), 3.58 (1H, dq, *J* 9.2, 7.1, CH(OCH_2CH_3)$_2$), 3.69 (1H, dq, *J* 9.2, 7.1, CH(OCH_2CH_3)$_2$), 3.74 (2H, d, *J* 13.9, N(CH_2Ph)$_2$), 3.78 (2H, d, *J* 13.9, N(CH_2Ph)$_2$), 4.58 (1H, d, *J* 4.3, C*H*(OEt)$_2$), 7.08–7.25 (15H, m, Ph); δ_C (100 MHz, $CDCl_3$), 23.0 (OCH_2CH_3), 23.2 (OCH_2CH_3), 40.3 (NCH(CH_2Ph)), 62.1 (N*C*H(CH_2Ph)), 67.9 (N(CH_2Ph)$_2$), 70.7 (OCH_2CH_3), 70.8 (OCH_2CH_3), 112.6 (*C*H(OEt)$_2$), 133.2 (Ph), 134.2 (Ph), 135.6 (Ph), 136.4 (Ph), 137.3 (Ph), 148.1 (Ph), 148.7 (Ph); IR (neat), ν_{max}/cm^{-1} 3026, 2974, 2927, 2871, 1495, 1453, 1118, 1061, 744, 698; HRMS (ES): 404.2583; calculated for $C_{27}H_{34}NO_2$: 404.2589; Microanalysis: found C 80.3, H 8.25, N 3.2; calculated for $C_{27}H_{33}NO_2$: C 80.36, H 8.24, N 3.47.

(*S*)-2-(*N*,*N*-Dibenzyl)amino-3-methylbutanal diethyl acetal, 35 (R = Pr^i). Typical procedure D was used with dimethyl sulfoxide (2.70 ml, 2.96 g, 37.8 mmol), oxalyl chloride (1.65 ml, 2.40 g, 18.9 mmol),-2-(*N*,*N*-dibenzyl)amino-3-methyl-1-butanol (4.89 g, 17.2 mmol), triethylamine (12.0 ml, 8.70 g, 86.0 mmol), triethyl orthoformate (28.6 ml, 25.5g, 172 mmol), and concentrated sulfuric acid (2.8 ml). The product was purified by silica gel flash chromatography (eluent: petroleum ether/ethyl acetate/triethylamine 89.5 : 10 : 0.5) to yield *the acetal* **35** (R = Pr^i) as a colourless oil (4.55g, 12.8 mmol, 75%). $[\alpha]_D$ −42.7 ($CHCl_3$, *c* 1.5); δ_H (500 MHz, $CDCl_3$) 0.83 (3H, d, *J* 6.7, NCH-CH(CH_3)$_2$), 0.98 (3H, d, *J* 6.8, NCHCH(CH_3)$_2$), 1.23 (3H, t, *J* 7.0, OCH_2CH_3), 1.25 (3H, t, *J* 7.0, OCH_2CH_3), 1.99–2.07 (1H, m, NCHC*H*(CH_3)$_2$), 2.45 (1H, dd, *J* 7.2, 4.5, NC*H*CH(CH_3)$_2$), 3.44 (1H, dq, *J* 9.2, 7.0, CH(OCH_2CH_3)$_2$), 3.53 (1H, dq, *J* 9.2, 7.0, CH(OCH_2CH_3)$_2$), 3.67 (1H, dq, *J* 9.2, 7.0, CH(OCH_2-CH_3)$_2$), 3.69 (1H, dq, *J* 9.2, 7.0, CH(OCH_2CH_3)$_2$), 3.71 (2H, d, *J* 13.7, N(CH_2Ph)$_2$), 3.91 (2H, d, *J* 13.7, N(CH_2Ph)$_2$), 4.69 (1H, d, *J* 4.5, C*H*(OEt)$_2$), 7.18–7.38 (10H, m, Ph); δ_C (125 MHz, $CDCl_3$), 15.5 (NCHCH(CH_3)$_2$), 15.6 (NCHCH(CH_3)$_2$) 20.8 (OCH_2CH_3), 20.9 (OCH_2CH_3), 27.4 (NCH*C*H(CH_3)$_2$), 55.7 (N(CH_2Ph)$_2$), 62.9 (OCH_2CH_3), 63.2 (N*C*HCH(CH_3)$_2$), 63.3 (OCH_2CH_3), 104.7 (*C*H(OEt)$_2$), 126.6 (Ph), 128.0 (Ph), 129.2 (Ph), 141.0 (Ph); IR (neat), ν_{max}/cm^{-1} 2974, 2924, 2870, 1494, 1454, 1373, 1165, 1123, 749, 698; MS (EI) *m*/*z* 355 (M$^+$, 0.1%), 253 (26), 252 (100), 91 (98); Microanalysis: found C 77.45, H 9.4, N 3.65; calculated for $C_{23}H_{33}NO_2$: C 77.70, H 9.36, N 3.94.

(*S*)-2-(*N*,*N*-Dibenzyl)aminopropanal diethyl acetal, 35 (R = Me).[30] Typical procedure D was used with dimethyl sulfoxide (2.47 ml, 2.72 g, 34.8 mmol), oxalyl chloride (1.52 ml, 2.21 g, 17.4 mmol),-2-(*N*,*N*-dibenzyl)amino-1-propanol (4.04 g, 15.8 mmol), triethylamine (11.0 ml, 8.00 g, 79.1 mmol), triethyl orthoformate (26.3 ml, 23.4 g, 158 mmol), and concentrated sulfuric acid (2.5 ml). The product was purified by silica gel flash chromatography (eluent: petroleum ether/ethyl acetate/triethylamine 89.5 : 10 : 0.5) to yield the acetal[30] **35** (R = Me) as a colourless oil (3.74 g, 11.4 mmol, 72%). $[\alpha]_D$ −11.7 ($CHCl_3$, *c* 1.2); δ_H (500 MHz, $CDCl_3$), 1.09 (3H, d, *J* 6.8, NCHCH_3), 1.16 (3H, t, *J* 7.0, OCH_2CH_3), 1.17 (3H, t, *J* 7.0, OCH_2CH_3), 2.88 (1H, dq, *J* 5.3, 6.8, NC*H*CH_3), 3.33 (1H, dq, *J* 9.2, 7.0, CH(OCH_2CH_3)$_2$), 3.46 (1H, dq, *J* 9.4, 7.0, CH(OCH_2CH_3)$_2$), 3.48 (1H, dq, *J* 9.2, 7.0, CH(OCH_2CH_3)$_2$), 3.53 (2H, d, *J* 13.8, N(CH_2Ph)$_2$), 3.70 (1H, dq, *J* 9.4, 7.0, CH(OCH_2CH_3)$_2$), 3.83 (2H, d, *J* 13.8, N(CH_2Ph)$_2$), 4.49 (1H, d, *J* 5.3, C*H*(OEt)$_2$), 7.17–7.38 (10H, m, Ph); δ_C (125 MHz, $CDCl_3$), 9.1 (NCHCH_3), 15.3 (OCH_2CH_3), 15.4 (OCH_2CH_3), 54.2 (N*C*HCH_3), 54.4 (N(CH_2Ph)$_2$), 61.7 (OCH_2CH_3), 63.2 (OCH_2CH_3), 105.7 (*C*H(OEt)$_2$), 126.6 (Ph), 128.1 (Ph), 128.7 (Ph), 140.8 (Ph); IR (neat), ν_{max}/cm^{-1} 2974, 1494, 1454, 1375, 1122, 1099, 1059, 1025, 747, 734, 699; MS (FAB) *m*/*z* 327 (M$^+$, 6%), 326 (24), 282 (21), 225 (20), 224 (100), 91 (96); Microanalysis: found C 77.05, H 8.9, N 4.25; calculated for $C_{21}H_{29}NO_2$: C 77.03, H 8.93, N 4.28.

(2*S*,3*R*)-2-(*N*,*N*-Dibenzyl)amino-3-ethoxy-1-phenylpentane, 36 (R = Bn). Typical procedure A was used with TMSOTf (293 µl, 360 mg, 1.62 mmol), −2-(*N*,*N*-dibenzylamino)-3-phenylpropanal diethyl acetal (218 mg, 540 µmol), and diethyl zinc (1.1M solution in toluene, 272 µl, 133 mg, 1.08 mmol). The product was purified by silica gel flash chromatography (eluent: petroleum ether/ethyl acetate/triethylamine 96.5 : 3 : 0.5) to yield *the ether* **36** (R = Bn) as a colourless oil and an inseparable mixture of two diastereoisomers (134 mg, 346 µmol, 64%, dr 95 : 5 by ^{1}H NMR). Major diastereoisomer: δ_H (400 MHz, $CDCl_3$), 0.71 (3H, t, *J* 7.4, CH(OEt)CH_2CH_3), 1.17 (3H, t, *J* 7.2, OCH_2CH_3), 1.43–1.55 (1H, m, CH(OEt)CH_2CH_3), 1.45–1.56 (1H, m, CH(OEt)CH_2CH_3), 2.89 (1H, dt, 2.7, 12.3, NC*H*-BnCH), 2.95 (1H, dd, *J* 8.6, 5.2, NCH(CH_2Ph), 2.99 (1H, dd, *J* 8.6, 12.3, NCH(CH_2Ph), 3.39–3.49 (2H, m, OCH_2CH_3), 3.57–3.64 (1H, m, C*H*(OEt)Et), 3.56 (2H, d, *J* 14.1, N(CH_2Ph)$_2$), 3.79 (2H, d, *J* 14.1, N(CH_2Ph)$_2$), 7.11–7.34 (15H, m, Ph); δ_C (100 MHz, $CDCl_3$), 10.1 (CH(OEt)CH_2CH_3), 15.8 (OCH_2-CH_3), 24.7 (CH(OEt)CH_2CH_3), 32.3 (NCH(CH_2Ph), 54.3 (N(CH_2Ph)$_2$), 60.9 (N*C*HBnCH), 64.8 (OCH_2CH_3), 80.9 (*C*H(OEt)Et), 125.5 (Ph), 126.5 (Ph), 128.0 (Ph), 128.7 (Ph), 129.2 (Ph), 129.7 (Ph), 140.3 (Ph), 141.8 (Ph); mixture of diastereoisomers (95 : 5): $[\alpha]_D$ −14.3 ($CHCl_3$, *c* 1.4); IR (neat), ν_{max}/cm^{-1} 2970, 2933, 1452, 1101, 1088, 700; HRMS (ES): 388.2630; calculated for $C_{27}H_{34}NO$: 388.2640; Microanalysis: found C 83.35, H 8.55, N 3.8; calculated for $C_{27}H_{33}NO$: C 83.74, H 8.59, N 3.62.

(3*S*,4*R*)-3-(*N*,*N*-Dibenzyl)amino-4-ethoxy-1-methylhexane, 36 (R = Pr^i). Typical procedure A was used with TMSOTf (501 µl, 615 mg, 2.77 mmol),-2-(*N*,*N*-dibenzyl)amino-3-methylbutanal diethyl acetal (328 mg, 922 µmol), and diethyl zinc (1.1M solution in toluene, 1.7 ml, 228 mg, 1.84 mmol). The product was purified by silica gel flash chromatography (eluent: petroleum ether/ethyl acetate/triethylamine 96.5 : 3 : 0.5) to yield *the ether* **36** (R = Bn) as a colourless oil and an inseparable mixture of two diastereoisomers (192 mg, 566 µmol, 61%, dr 93 : 7 by ^{1}H NMR). Major diastereoisomer: δ_H (500 MHz, $CDCl_3$) 0.76 (3H, t, *J* 7.5, CH(OEt)CH_2CH_3), 0.95 (3H, d, *J* 6.7, NCHCH(CH_3)$_2$), 1.07 (3H, d, *J* 6.8, NCHCH(CH_3)$_2$), 1.17 (3H, t, *J* 7.0, OCH_2CH_3), 1.54–1.61 (1H, m, CH(OEt)-CH_2CH_3), 1.69–1.76 (1H, m, CH(OEt)CH_2CH_3), 2.15–2.23 (1H, m, NCHC*H*(CH_3)$_2$), 2.33 (1H, dd, *J* 6.3, 4.4, NC*H*-CH(CH_3)$_2$), 3.37 (1H, dq, 8.8, 7.0, OCH_2CH_3), 3.47–3.50 (1H, m, C*H*(OEt)Et), 3.50 (2H, d, *J* 13.8, N(CH_2Ph)$_2$), 3.57 (1H, dq, 8.7, 7.0, OCH_2CH_3), 3.80 (2H, d, *J* 13.8, N(CH_2Ph)$_2$), 7.17–7.38 (10H, m, Ph); δ_C (125 MHz, $CDCl_3$), 10.2 ((NCHCH(CH_3)$_2$), 15.8 (NCHCH(CH_3)$_2$), 20.9 (CH(OEt)CH_2CH_3), 22.7 (OCH_2-CH_3), 25.1 (CH(OEt)CH_2CH_3), 26.6 (NCH*C*H(CH_3)$_2$), 54.8 (N(CH_2Ph)$_2$), 63.5 (N*C*HCH(CH_3)$_2$), 64.1 (OCH_2CH_3), 81.8 (*C*H(OEt)Et), 126.7 (Ph), 128.0 (Ph), 129.1 (Ph), 1406 (Ph); Mixture of diastereoisomers (93 : 7): $[\alpha]_D$ −8.0 ($CHCl_3$, *c* 1.0); IR (neat), ν_{max}/cm^{-1} 2971, 2932, 2874, 1494, 1453, 1115, 1074, 733, 698; MS (ES) *m*/*z* 341 (M$^+$2, 15%), 340 (M$^+$1, 100%).

(2*S*,3*R*)-2-(*N*,*N*-Dibenzyl)amino-3-ethoxypentane, 36 (R = Me). Typical procedure A was used with TMSOTf (474 µl, 582 mg, 2.62 mmol), −2-(*N*,*N*-dibenzyl)aminopropanal diethyl acetal (286 mg, 873 µmol), and diethyl zinc (1.1M solution in toluene, 1.6 ml, 216 mg, 1.75 mmol). The product was purified by silica gel flash chromatography (eluent: petroleum ether/ethyl acetate/triethylamine 96.5 : 3 : 0.5) to yield *the ether* **36** (R = Me) as a colourless oil and an inseparable mixture of two

diastereoisomers (210 mg, 674 μmol, 77%, dr 94 : 6 by ^{1}H NMR). Major diastereoisomer: δ_H (500 MHz, $CDCl_3$), 0.66 (3H, t, *J* 7.4, CH(OEt)CH_2CH_3), 1.10 (3H, d, *J* 6.7, NCHCH_3), 1.14 (3H, t, *J* 7.0, OCH_2CH_3), 1.49–1.56 (1H, m, CH(OEt)-CH_2CH_3), 1.68–1.75 (1H, m, CH(OEt)CH_2CH_3), 2.67 (1H, quin, *J* 6.7, NC*H*CH_3), 3.20–3.26 (1H, m, C*H*(OEt)Et), 3.38–3.43 (1H, m, OCH_2CH_3), 3.43 (2H, d, *J* 14.1, N($CH_2Ph)_2$), 3.51–3.58 (1H, m, OCH_2CH_3), 3.72 (2H, d, *J* 13.8, N($CH_2Ph)_2$), 7.13–7.38 (10H, m, Ph); δ_C (125 MHz, $CDCl_3$), 8.4 (CH(OEt)CH_2CH_3), 9.0 (NCHCH_3), 15.7 (OCH_2CH_3), 24.0 (CH(OEt)CH_2CH_3), 54.4 (N($CH_2Ph)_2$), 54.9 (NCHCH$_3$), 65.5 (OCH_2CH_3), 83.1 (*C*H(OEt)Et), 126.7 (Ph), 128.1 (Ph), 128.8 (Ph), 140.4 (Ph); mixture of diastereoisomers (94 : 6): $[\alpha]_D$ +14.5 ($CHCl_3$, *c* 1.1); IR (neat), ν_{max}/cm^{-1} 2971, 2932, 2874, 1494, 1453, 1116, 1075, 909, 735, 698; MS (EI) *m*/*z* 311 (M$^+$, 0.5%), 296 (1.4), 225 (20), 224 (100), 91 (94).

1-((1*R*,2*S*)-2-(*N*,*N*-Dibenzylamino)-1-ethoxy-3-phenylpropyl)-1*H*-pyrimidine-2,4-dione, 37 (R = Bn). Typical procedure B was used with TMSOTf (179 μl, 220 mg, 989 μmol),-2-(*N*,*N*-dibenzylamino)-3-phenylpropanal diethyl acetal (133 mg, 330 μmol), and bis(*O*-trimethylsilyl)uracil (169 mg, 660 μmol). The product was purified by silica gel flash chromatography (eluent: gradient of petroleum ether/ethyl acetate/triethylamine 79.5 : 20 : 0.5–59.5 : 40 : 0.5) to yield *the uracil derivative* **37** (R = Bn) as colourless plates and a single diastereoisomer (109 mg, 232 μmol, 70%, de >98%). Mp 77–79 °C; $[\alpha]_D$ +63.3 ($CHCl_3$, *c* 1.2); δ_H (500 MHz, $CDCl_3$), 1.24 (3H, *J* 7.0, OCH_2CH_3), 2.91 (1H, dd, *J* 14.8, 11.2, NC*H*Bn), 3.19–3.24 (2H, m, NCH(CH_2Ph)), 3.33 (1H, dq, *J* 9.5, 7.0, OCH_2CH_3), 3.45 (1H, dq, *J* 9.5, 7.0, OCH_2CH_3), 3.56 (2H, d, *J* 13.7, N($CH_2Ph)_2$), 4.14 (2H, d, *J* 13.7, N($CH_2Ph)_2$), 5.32 (1H, d, *J* 4.0, C*H*(*uracil*)OEt), 5.65 (1H, dd, *J* 8.0, 2.2, *uracil*-C*H*), 7.11–7.34 (15H, m, Ph), 7.37 (1H, d, *J* 8.0, *uracil*-C*H*); δ_C (125 MHz, $CDCl_3$), 15.0 (OCH_2CH_3), 31.1 (NCH(CH_2Ph)), 55.6 (N($CH_2Ph)_2$), 60.1 (NCH(CH_2Ph)), 65.8 (OCH_2CH_3), 87.2 (*C*H(*uracil*)OEt), 100.4 (*uracil*-*C*H), 126.6 (Ph), 127.2 (Ph), 128.4 (Ph), 128.5 (Ph), 128.7 (Ph), 128.9 (Ph), 138.5 (Ph), 139.2 (Ph), 141.2 (*uracil*-*C*H), 149.8 (*uracil*-*C*O), 163.2 (*uracil*-*C*O); IR (neat), ν_{max}/cm^{-1} 3060, 3029, 2977, 1699, 1495, 1456, 1102, 732, 699; MS (EI) *m*/*z* 469 (M$^+$, 0.2%), 378 (17), 301 (56), 300 (93), 181 (13), 91 (100); HRMS (ES): 492.2273; calculated for $C_{29}H_{31}N_3O_3Na$: 492.2263; structure confirmed by X-ray crystallographic analysis[10] and data has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 153574.

1-((1*R*,2*S*)-2-(*N*,*N*-Dibenzylamino)-1-ethoxy-3-methylbutyl)-1*H*-pyrimidine-2,4-dione, 37 (R = Pr^i). Typical procedure B was used with TMSOTf (505 μl, 621 mg, 2.79 mmol),-2-(*N*,*N*-dibenzyl)amino-3-methylbutanal diethyl acetal (331 mg, 931 μmol), and bis(*O*-trimethylsilyl)uracil (477 mg, 1.86 mmol). The product was purified by silica gel flash chromatography (eluent: gradient of petroleum ether/ethyl acetate/triethylamine 69.5 : 30 : 0.5 to ethyl acetate) to yield *the uracil derivative* **37** (R = Pr^i) as a colourless plates and an inseparable mixture of two diastereoisomers (304 mg, 721 μmol, 76%, dr 89 : 11 by ^{1}H NMR); major diastereoisomer (1*R*,2*S*): δ_H (500 MHz, $CDCl_3$), 1.00 (3H, d, *J* 6.7, NCHCH($CH_3)_2$), 1.17 (3H, d, *J* 6.8, NCH-CH($CH_3)_2$), 1.24 (3H, t, *J* 7.0, OCH_2CH_3), 2.16–2.23 (1H, m, NCHC*H*($CH_3)_2$), 2.68 (3H, dd, *J* 6.9, 4.2, NC*H*CH($CH_3)_2$), 3.42–3.52 (2H, m, OCH_2CH_3), 3.74 (2H, d, *J* 13.1, N($CH_2Ph)_2$), 4.07 (2H, d, *J* 13.1, N($CH_2Ph)_2$), 5.66 (1H, d, *J* 8.0, *uracil*–C*H*), 5.68 (1H, d, *J* 4.2, C*H*(OEt)N), 7.15–7.31 (10H, m, Ph), 7.40 (1H, d, *J* 8.0, *uracil*–C*H*); δ_C (125 MHz, $CDCl_3$), 15.1 (NCH-CH($CH_3)_2$), 21.2 (NCHCH($CH_3)_2$), 22.1 (OCH_2CH_3), 27.8 (NCHCH($CH_3)_2$), 56.5 (N($CH_2Ph)_2$), 63.2 (NCH^{i}Pr), 65.4 (OCH_2CH_3), 87.3 (*C*H(OEt)N), 100.9 (*uracil*–*C*H), 127.1 (Ph), 128.3 (Ph), 129.2 (Ph), 139.5 (Ph), 141.1 (*uracil*–*C*H), 150.2 (*uracil*–*C*O), 163.6 (*uracil*–*C*O); Mixture of diastereoisomers (89 : 11): mp 68–71 °C; $[\alpha]_D$ +60.0 ($CHCl_3$, *c* 1.0); IR (neat), ν_{max}/cm^{-1} 2976, 1698, 1455, 1266, 1153, 1093, 737, 701; MS (ES) *m*/*z* 421 (M$^+$, 0.1%), 309 (10), 280 (10), 253 (24), 252 (82), 92 (17), 91 (100).

1-((1*R*,2*S*)-2-(*N*,*N*-Dibenzylamino)-1-ethoxypropyl)-1*H*-pyrimidine-2,4-dione, 37 (R = Me). Typical procedure B was used with, TMSOTf (464 μl, 570 mg, 2.57 mmol), 2-(*N*,*N*-dibenzyl)-aminopropanal diethyl acetal (286 mg, 873 μmol), and bis(*O*-trimethylsilyl)uracil (438 mg, 1.71 mmol). The product was purified by silica gel flash chromatography (eluent: gradient of petroleum ether/ethyl acetate/triethylamine 69.5 : 30 : 0.5 to ethyl acetate) to yield *the uracil derivative* **37** (R = Me) as colourless needles and an inseparable mixture of two diastereoisomers (240 mg, 610 μmol, 71%, dr 55 : 45 by ^{1}H NMR); major diastereoisomer (1*R*,2*S*): δ_H (500 MHz, $CDCl_3$), 1.20 (3H, d, *J* 7.0, NCHCH_3), 1.24 (3H, t, *J* 7.0, OCH_2CH_3), 2.96–3.02 (1H, m, NC*H*CH_3), 3.41 (2H, d, *J* 13.8, N($CH_2Ph)_2$), 3.48 (2H, q, *J* 7.0, OCH_2CH_3), 4.01 (2H, d, *J* 13.8, N($CH_2Ph)_2$), 5.41 (1H, d, *J* 4.4, C*H*(OEt)N), 5.74 (1H, d, *J* 8.0, *uracil*-C*H*), 7.18–7.31 (10H, m, Ph), 7.44 (1H, d, *J* 8.0, *uracil*-C*H*); δ_C (125 MHz, $CDCl_3$), 9.4 (NCHCH_3), 14.8 (OCH_2CH_3), 54.3 (NCHCH$_3$), 55.3 (N($CH_2Ph)_2$), 66.0 (OCH_2CH_3), 89.1 (*C*H(OEt)N), 100.7 (*uracil*-*C*H), 127.0 (Ph), 128.4 (Ph), 128.5 (Ph), 139.5 (Ph), 141.1 (*uracil*-*C*H), 150.2 (*uracil*-*C*O), 163.2 (*uracil*-*C*O); minor diastereoisomer (1*S*,2*S*): δ_H (500 MHz, $CDCl_3$), 1.13 (3H, t, *J* 7.0, OCH_2CH_3), 1.26 (3H, d, *J* 6.5, NCHCH_3), 2.84–2.90 (1H, m, NC*H*CH_3), 3.28 (2H, d, *J* 13.2, N($CH_2Ph)_2$), 3.45 (1H, dq, *J* 9.2, 7.0, OCH_2CH_3), 3.52 (1H, dq, *J* 9.2, 7.0, OCH_2CH_3), 3.72 (2H, d, *J* 13.2, N($CH_2Ph)_2$), 5.51 (1H, d, *J* 8.0, *uracil*-C*H*), 5.73 (1H, d, *J* 9.1, C*H*(OEt)N), 6.58 (1H, d, *J* 8.0, *uracil*-C*H*), 7.18–7.31 (10H, m, Ph); δ_C (125 MHz, $CDCl_3$), 8.4 (NCHCH_3), 14.8 (OCH_2CH_3), 53.9 (NCHCH$_3$), 55.1 (N($CH_2Ph)_2$), 65.1 (OCH_2CH_3), 85.7 (*C*H(OEt)N), 102.3 (*uracil*-*C*H), 127.2 (Ph), 128.3 (Ph), 129.0 (Ph), 138.9 (Ph), 140.3 (*uracil*-*C*H), 151.4 (*uracil*-*C*O), 163.0(*uracil*-*C*O); mixture of diastereoisomers (55 : 45): mp 48–51 °C; $[\alpha]_D$ +8.60 ($CHCl_3$, *c* 1.4); IR (neat), ν_{max}/cm^{-1} 3190, 3061, 2977, 2937, 2808, 1699, 1495, 1452, 1385, 1265, 1151, 1085, 809, 743, 701; MS (EI) *m*/*z* 392 (M$^+$, 0.2%), 281 (5), 225 (39), 224 (100), 181 (17), 91 (99); HRMS (ES): 416.1964; calculated for $C_{23}H_{27}N_3O_3Na$: 416.1950.

1-((1*R*,2*S*)-2-(*N*,*N*-Dibenzylamino)-1-ethoxy-3-phenylpropyl)-1*H*-pyridin-2-one, 38 (R = Bn). Typical procedure B was used with TMSOTf (452 μl, 555 mg, 2.50 mmol), 2-(*N*,*N*-dibenzylamino)-3-phenylpropanal diethyl acetal (336 mg, 833 μmol), and 2-trimethylsilyloxypyridine (279 mg, 1.67 mmol). The product was purified by silica gel flash chromatography (eluent: gradient of petroleum ether/ethyl acetate/triethylamine 69 : 30 : 1–49 : 50 : 1) to yield **38** (R = Bn) as colourless plates and an inseparable mixture of two diastereoisomers (340 mg, 715 μmol, 89%, dr 95 : 5 by ^{1}H NMR). Major diastereoisomer: δ_H (500 MHz, $CDCl_3$), 1.23 (3H, *J* 7.0, OCH_2CH_3), 2.81 (1H, dd, *J* 13.9, 8.4, NCH(CH_2Ph)), 3.11 (1H, dd, *J* 13.9, 6.3, NCH(CH_2Ph)), 3.28 (1H, ddd, *J* 8.4, 6.3, 5.2, NC*H*(CH_2Ph)), 3.37 (1H, q, *J* 7.0, OCH_2CH_3), 3.38 (1H, q, *J* 7.0, OCH_2CH_3), 3.67 (2H, d, *J* 13.9, N($CH_2Ph)_2$), 4.12 (2H, d, *J* 13.9, N($CH_2Ph)_2$), 5.92 (1H, d, *J* 5.2, C*H*(*py*)OEt), 6.17 (1H, dt, *J* 1.3, 6.7, *py*5-C*H*), 6.35 (1H, ddd, *J* 9.1, 1.3, 0.6, *py*3-C*H*), 7.04 (1H, dd, *J* 6.8, 1.3, *py*4-C*H*), 7.15–7.28 (15H, m, Ph), 7.46 (1H, ddd, *J* 7.0, 2.1, 0.6, *py*6-C*H*); δ_C (125 MHz, $CDCl_3$), 15.2 (OCH_2CH_3), 31.8 (NCH(CH_2Ph)), 55.3 (N($CH_2Ph)_2$), 60.4 (NCH(CH_2Ph)), 65.3 (OCH_2CH_3), 86.6 (*C*H(py)OEt), 105.0 (py5-*C*H), 120.6 (py3-*C*H), 126.1 (py4-*C*H), 126.8 (Ph), 128.2 (Ph), 128.3 (Ph), 128.4 (Ph), 129.1 (Ph), 133.8 (Ph), 138.9 (Ph), 139.1 (Ph), 139.6 (py6-*C*H), 162.5 (py2-*C*O); mixture of diastereoisomers (95 : 5): $[\alpha]_D$ +150.0 ($CHCl_3$, *c* 0.8); IR (neat), ν_{max}/cm^{-1} 3063, 3027, 2977, 1660, 1587, 1538, 1495, 1454, 1139, 1103, 1077, 910, 734, 699; MS (EI) *m*/*z* 377 (M + 1, 45%), 282

(100); microanalysis: found C 79.35, H 7.2, N 6.25; calculated for $C_{30}H_{32}N_2O_2$: C 79.61, H 7.13, N 6.19.

1-((1*R*,2*S*)-2-(*N*,*N*-Dibenzylamino)-1-ethoxypropyl)-1*H*-pyridin-2-one, 38 (R = Me). Typical procedure B was used with TMSOTf (521 μl, 639 mg, 2.88 mmol), 2-(*N*,*N*-dibenzyl)-aminopropanal diethyl acetal (314 mg, 959 μmol), and 2-trimethylsilyloxypyridine (321 mg, 1.92 mmol). Analysis of crude ^{1}H NMR spectra indicated a 54 : 46 mixture of diastereoisomers. The product was purified by silica gel flash chromatography (eluent: petroleum ether/ethyl acetate/triethylamine 69 : 30 : 1) to yield the major diastereoisomer of *the pyridone derivative* (1*R*,2*S*)-**38** (R = Me) as a colourless oil (185 mg, 491 μmol, 51%), and the minor diastereoisomer (1*S*,2*S*)-**38** (R = Me) as a colourless oil (130 mg, 345 μmol, 36%). Major diastereoisomer (1*R*,2*S*)-**38** (R = Me) $[\alpha]_D$ +187.4 ($CHCl_3$, *c* 1.9); δ_H (500 MHz, $CDCl_3$), 1.11 (3H, d, *J* 7.0, NCHCH_3), 1.23 (3H, t, *J* 7.0, OCH$_2$CH_3), 3.03 (1H, ddd, *J* 13.9, 7.0, 5.6, NC*H*CH$_3$), 3.45 (2H, q, *J* 7.0, OCH_2CH$_3$), 3.54 (2H, d, *J* 14.1, N(CH_2Ph)$_2$), 4.03 (2H, d, *J* 14.1, N(CH_2Ph)$_2$), 5.99 (1H, d, *J* 5.6, C*H*(OEt)N), 6.21 (1H, dt, *J* 1.3, 6.7, *py*5-C*H*), 6.41 (1H, ddd, *J* 9.2, 1.3, 0.7, *py*3-C*H*), 7.17–7.32 (11H, m, Ph, *py*4-C*H*), 7.47 (1H, ddd, *J* 6.9, 2.1, 0.7, *py*6-C*H*); δ_C (125 MHz, $CDCl_3$), 10.3 (NCHCH_3), 15.0 (OCH$_2$CH_3), 55.0 (N(CH_2Ph)$_2$), 55.2 (NCHCH$_3$), 65.4 (OCH_2CH$_3$), 87.7 (*C*H(OEt)N), 105.2 (*py*5-*C*H), 120.6 (*py*3-*C*H), 126.7 (Ph), 128.2 (Ph), 128.3 (Ph), 133.7 (*py*4-*C*H), 139.0 (Ph), 140.1 (*py*6-*C*H), 162.6 (*py*2-*C*O); IR (neat), ν_{max}/cm^{-1} 2807, 1674, 1599, 1538, 1495, 1455, 1245, 1141, 1075, 1028, 910, 857, 840, 751, 699; MS (ES) *m*/*z* 454 (M^+2, 32%), 453 (M^+, 100%), 358 (60); Microanalysis: found C 76.5, H 7.7, N 7.6; calculated for $C_{24}H_{28}N_2O_2$: C 76.55, H 7.49, N 7.44. Minor diastereoisomer (1*S*,2*S*)-**38** (R = Me): $[\alpha]_D$ −123.1 ($CHCl_3$, *c* 1.3); δ_H (500 MHz, $CDCl_3$), 1.10 (3H, t, *J* 7.0, OCH$_2$CH_3), 1.27 (3H, d, *J* 6.5, NCHCH_3), 2.92 (1H, ddd, *J* 15.0, 8.5, 6.5, NC*H*CH$_3$), 3.31 (2H, d, *J* 13.3, N(CH_2Ph)$_2$), 3.41 (1H, dq, *J* 9.7, 7.0, OCH_2-CH$_3$), 3.50 (1H, dq, *J* 9.7, 7.0, OCH_2CH$_3$), 3.74 (2H, d, *J* 13.3, N(CH_2Ph)$_2$), 6.06 (1H, dt, *J* 1.2, 6.7, *py*5-C*H*), 6.27 (1H, d, *J* 8.5, C*H*(OEt)N), 6.54 (1H, ddd, *J* 9.2, 1.3, 0.7, *py*3-C*H*), 6.81 (1H, ddd, *J* 7.0, 2.1, 0.6, *py*4-C*H*), 7.09–7.26 (10H, m, Ph), 7.34 (1H, ddd, *J* 9.2, 6.5, 2.1, *py*6-C*H*); δ_C (125 MHz, $CDCl_3$), 8.7 (NCHCH_3), 14.9 (OCH$_2$CH_3), 53.9 (N(CH_2Ph)$_2$), 55.7 (NCHCH$_3$), 64.8 (OCH_2CH$_3$), 84.8 (*C*H(OEt)N), 105.7 (*py*5-*C*H), 120.4 (*py*3-*C*H), 126.8 (Ph), 128.1 (Ph), 129.1 (Ph), 133.9 (*py*4-*C*H), 139.1 (Ph), 139.5 (*py*6-*C*H), 163.2 (*py*-*C*O).

(2*S*,3*S*)-2-(*N*,*N*-Dibenzyl)amino-1-phenyl-3-pentanol, 39.[19] A solution of dimethyl sulfoxide (3.20 ml, 3.52g, 45.1 mmol) in CH_2Cl_2 (10 ml) was added dropwise over 3 min to a stirred solution of oxalyl chloride (1.97 ml, 2.86g, 22.6 mmol) in CH_2Cl_2 (50 ml) at −61°C (cardice/chloroform bath). After 5 min of stirring, a solution of 2-(*N*,*N*-dibenzylamino)-3-phenyl-1-propanol **34** (R = Bn) (6.80g, 20.5 mmol) in CH_2Cl_2 (25 ml) was added dropwise over 5 min. After a further 30 min, triethylamine (14.3 ml, 10.4g, 103 mmol) was added, and the mixture stirred for 1 h at −61°C, then 2 h at ambient temperature. Water (120 ml) was added, and the aqueous layer extracted with CH_2Cl_2 (3 × 100 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*, to yield-2-(*N*,*N*-dibenzyl)amino-3-phenylpropanal (6.15g, 18.7 mmol, 91%). To a solution of the crude aldehyde (601 mg, 1.80 mmol) in toluene (5 ml) at 0 °C was added diethyl zinc (1.1M solution in toluene, 3.57 ml of solution, 490 mg, 3.96 mmol). After stirring at 0 °C for 2 h then ambient temperature for 15 h, a saturated solution of ammonium chloride (30 ml) was added, and the product extracted with diethyl ether (3 × 25 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified by silica gel flash chromatography (eluent: hexane/ethyl acetate/triethylamine 89.5 : 10 : 0.5) to yield the alcohol[19] **39** (505 mg, 1.39 mmol, 77%) as a colourless oil. δ_H (300 MHz, $CDCl_3$), 0.81 (3H, t, *J* 7.3, CH$_2$CH_3), 1.06 (1H, m, CH_2CH$_3$), 1.46 (1H, m, CH_2CH$_3$), 2.65 (1H, dd, *J* 14.3, 6.0, NCH(CH_2Ph)), 2.88 (1H, m, NC*H*(CH$_2$Ph)), 3.07 (1H, dd, *J* 14.3, 6.5, NCH(CH_2Ph)), 3.35 (2H, d, *J* 13.2, N(CH_2Ph)$_2$), 3.52 (1H, m, C*H*(OH)Et), 3.89 (2H, d, *J* 13.2, N(CH_2Ph)$_2$), 4.47 (1H, s, O*H*), 7.10–7.40 (15H, m, Ph).

(2*S*,3*S*)-2-(*N*,*N*-dibenzyl)amino-3-ethoxy-1-phenylpentane, 41. To a solution of (2*S*,3*S*)-2-(*N*,*N*-dibenzyl)amino-1-phenyl-3-pentanol (**39**) (93 mg, 259 μmol) in THF (5 ml) was added sodium hydride (31 mg, 1.30 mmol), followed by ethyl iodide (208 μl, 406 mg, 2.60 mmol), and the mixture heated under reflux for 20 h. Wet THF (20 ml) was added, then the solvent removed *in vacuo*. Water (20 ml) was added and the product extracted with diethyl ether (3 × 25 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified by silica gel flash chromatography (eluent: hexane/ethyl acetate/triethylamine 96.5 : 3 : 0.5) to yield *the ether* **41** as a colourless oil (64 mg, 166 μmol, 64%). δ_H (500 MHz, $CDCl_3$), 0.39 (3H, t, *J* 7.5, CH$_2$CH_3), 1.17 (3H, t, *J* 7.0, OCH$_2$CH_3), 1.54–1.60 (1H, m, CH_2CH$_3$), 1.69–1.74 (1H, m, CH_2CH$_3$), 2.82–2.85 (1H, m, NC*H*(CH$_2$Ph)), 2.89 (1H, dt, *J* 7.8, 5.1, C*H*(OEt)Et), 2.96 (1H, dd, *J* 13.1, 9.4, NCH(CH_2Ph)), 3.07 (1H, dd, *J* 13.1, 4.9, NCH(CH_2Ph)), 3.19 (1H, dq, *J* 8.9, 7.0, OCH_2CH$_3$), 3.48 (2H, d, *J* 13.5, N(CH_2Ph)$_2$), 3.50 (1H, dq, *J* 8.9, 7.0, OCH_2CH$_3$), 4.15 (2H, *J* 13.5, NCH_2Ph)$_2$), 7.10–7.35 (15H, m, Ph); δ_C (125 MHz, $CDCl_3$), 10.0 (CH$_2$CH_3), 15.9 (OCH$_2$CH_3), 23.1 (CH_2CH$_3$), 30.1 (OCH_3CH$_3$), 55.5 (N(CH_2Ph)$_2$), 60.2 (NCH(CH$_2$Ph)), 65.4 (NCH(CH_2Ph)), 82.3 (*C*H(OEt)Et), 125.6 (Ph), 126.6 (Ph), 128.0 (Ph), 128.2 (Ph), 129.1 (Ph), 129.3 (Ph), 140.9 (Ph), 141.4 (Ph); MS (ES) *m*/*z* 388 (M + 1).

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