Alkylation of chiral 2-(aminomethyl)oxazolines†

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Chiral 2-(aminomethyl)oxazolines 3 and 7, in which the heterocycle is derived from (*R*)-phenylglycinol, are synthesized and studied in alkylation reactions involving strong base and alkyl halides. The tertiary amine derivative 3 is alkylated efficiently at the α-carbon centre with no stereochemical induction, while the tertiary carbamate 7 is alkylated in moderate yield and reasonable diastereomeric excess. The stereochemical control observed in the latter case can be explained by the preferred formation of an *E*-enolate during the deprotonation step by prior complexation of the carbamate carbonyl group to the base.

Oxazolines have become established as highly versatile compounds in organic synthesis.[1,2] The heterocyclic system serves as a latent function which can be transformed into a variety of other functional groups, while most of the chemical manipulations involve development of substituents borne at the 2-position.[3] One of the key features of the oxazoline system is the stabilization of a carbanion generated at the α-centre of a 2-alkyl derivative, and the subsequent reactions of such carbanions with a variety of electrophilic reagents. Following the pioneering work of Meyers, this reactivity has been exploited extensively in asymmetric synthesis.[1] Despite this large corpus, however, there is a scarcity of studies on the reactivity of 2-alkyloxazolines bearing a heteroatom at the α-carbon. A few rare reports have appeared on the alkylation of oxazolines bearing oxymethyl,[4,5] thiomethyl,[6,7] chloromethyl[8,9] and selenomethyl[10] substituents at *C*2. The preparation of some 2-(aminomethyl)oxazolines has been described,[11] but no successful *C*-alkylation reactions have been reported in the literature so far.[12,13] This is rather curious, in view of the obvious potential of these compounds for the asymmetric synthesis of amino acids, amino alcohols, *etc*.

We became interested in the reactivity of such compounds as an extension of our own work on the alkylation of α-amino nitrile systems.[14–18] Previously, we have adapted α-amino nitriles for asymmetric synthesis by incorporating the amino group in a chiral oxazoline (Fig. 1).[19] The 2-(aminomethyl)oxazoline structure appeared to be an interesting complement, in which the heterocycle can be deemed to represent a chiral adaptation of the nitrile group. In this article we describe the preparation of some compounds of this type and present our observations on their metallation–alkylation reactions with simple electrophiles.[20]

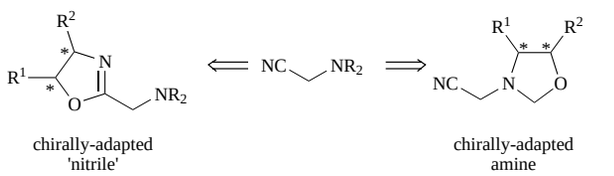
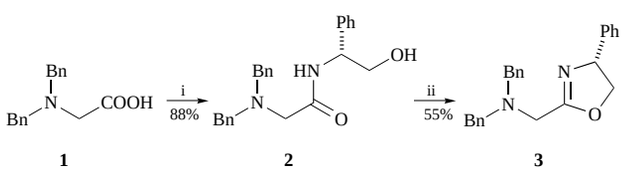
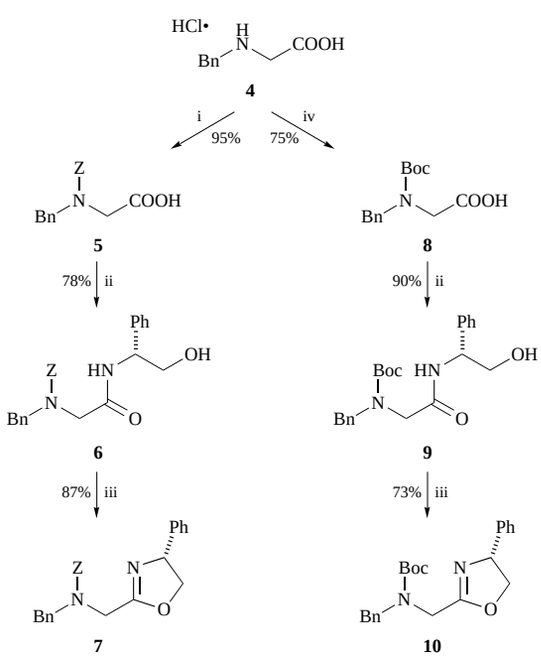


Fig. 1 Chiral adaptation of α-amino nitriles



Scheme 1 *Reagents and conditions:* i, Bu^{i}OCOCl, *N*-methylmorpholine, THF, −15 °C, then (*R*)-phenylglycinol; ii, Ph_3P, DEAD, THF



Scheme 2 *Reagents and conditions:* i, ZCl, $NaHCO_3$, H_2O; ii, Bu^{i}OCOCl, *N*-methylmorpholine, THF, −15 °C, then (*R*)-phenylglycinol; iii, $Et_3NSO_2NCOOMe$, THF, reflux; iv, Boc_2O, NaOH, dioxane–H_2O

Results and discussion

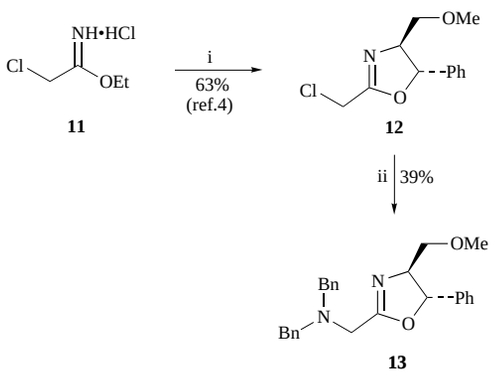
Preparation of aminomethyloxazolines

We decided to investigate the reactivity of two types of 2-(aminomethyl)oxazoline, namely tertiary amine derivatives and tertiary carbamate derivatives. As the amino alcohol precursor for the heterocycle, we selected (*R*)-phenylglycinol, a chiral auxiliary which we have found convenient in previous work.[19] For most of the alkylation studies, therefore, the oxazolines **3** and **7** were the substrates of choice and were prepared by cyclodehydration of the corresponding amides as shown in Schemes 1 and 2. *N*,*N*-Dibenzylglycine **1** (prepared from

† The term oxazoline has been superseded; 4,5-dihydrooxazole is the preferred name. IUPAC names are given in the Experimental section.

glycine)[21] was condensed with (*R*)-phenylglycinol using standard peptide coupling techniques (isobutyl chloroformate, *N*-methylmorpholine)[22] to give amide **2** in 88% yield. Cyclodehydration of **2** was not particularly efficient; the use of Burgess' salt, often the reagent of choice for such a transformation,[13,23] gave a low yield of **3** (*ca.* 25%) along with several other unidentified by-products. Oxazoline formation was best achieved (55% yield) using the Mitsunobu combination (Ph_3P–DEAD).[24] The preparation of carbamate **7** was more straightforward (Scheme 2); *N*-benzylglycine hydrochloride **4** (prepared from **1**)[21] was treated with benzyl chloroformate to give the fully protected glycine **5**, which was coupled with (*R*)-phenylglycinol as above to give amide **6**. In contrast with **2**, this compound underwent smooth cyclization with Burgess' reagent to give **7** as the only product, obtained in 64% overall yield for three steps requiring no chromatographic purification.

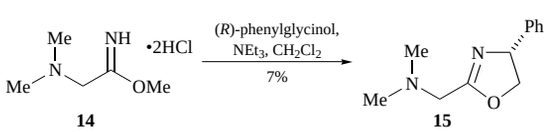
For comparison purposes, we also prepared samples of *tert*-butyl carbamate **10**, dibenzylamine **13** incorporating a 'Meyers-type' chiral oxazoline and dimethylamine **15**, using adaptations of the above schemes where possible. Thus the carbamate **10** was prepared *via* **8** and **9** in an analogous fashion to **7** (Scheme 2), except that Boc was substituted for the Z group (yield 49% for three steps). The precursor for the Meyers-type reagent (Scheme 3), (chloromethyl)oxazoline **12**, was prepared from



11 **12** **13**

Scheme 3 *Reagents and conditions:* i, (1*S*,2*S*)-2-amino-3-methoxy-1-phenylpropanol, Et_3N, CH_2Cl_2; ii, dibenzylamine, Et_3N, DMF

amidate hydrochloride **11** and (1*S*,2*S*)-2-amino-3-methoxy-1-phenylpropanol in 63% yield following the literature procedure.[4] Reaction of **12** with dibenzylamine gave the required product **13** in acceptable yield. For the synthesis of the dimethyl analogue **15**, we were unable to obtain any condensation product from (*R*)-phenylglycinol and *N*,*N*-dimethylglycine under standard conditions,[25] so an alternative method was sought (Scheme 4). Amidate dihydrochloride **14** was obtained



14 **15**

Scheme 4

from (dimethylamino)acetonitrile according to a literature procedure.[26] Treatment of this material with (*R*)-phenylglycinol in the presence of triethylamine gave a poor yield of oxazoline **15**, which was nonetheless sufficient for the purposes required here.

Alkylation of tertiary amine derivatives

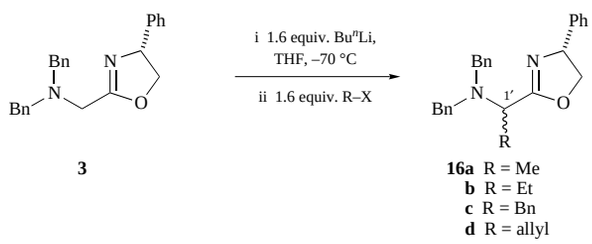
The bulk of the work was carried out on oxazoline **3**. Preliminary studies showed that treatment with 1.0 equiv. of strong base resulted in inefficient deprotonation. Thus, when a THF solution of **3** at −70 °C was treated with 1 equiv. of Bu^{n}Li, followed by an excess of D_2O, the recovered oxazoline was only *ca.* 10% deuteriated. The use of other strong bases (LDA, Bu^{s}Li) or the addition of complexing additives (HMPA, TMEDA) gave no improvement on this result. Much better results were obtained when >1.5 equiv. of Bu^{n}Li were used: in such cases, deuteriation of **3** was quantitative (as determined by ^{1}H NMR and mass spectroscopy). On this basis, the use of 1.6 equiv. of Bu^{n}Li in THF at −70 °C was considered the 'standard' deprotonating conditions for **3**.

Table 1 Alkylation of tertiary amine oxazolines[a]

Entry	Oxazoline	Electrophile	Product	Yield (%)[b]	Diastereomeric ratio[c]
1	**3**	MeI	**16a**	92	54:46
2		EtI	**16b**	67	53:47
3		$PhCH_2Br$	**16c**	71	54:46
4		allyl Br	**16d**	95	50:50
5		Pr^i Br	—	—[e]	—
6		MeI[d]	**16a**	20	50:50
7	**15**	MeI	**17**	47	50:50
8	**13**	MeI	**18**	65	59:41

[a] See text for standard conditions. [b] Isolated yields are quoted. [c] Determined on crude reaction mixtures immediately after work up; estimated error ±3%. [d] 0.95 equiv. of base used. [e] Starting material (84%) was recovered.

Deprotonation–alkylation reactions of **3** were then investigated using simple electrophiles [Scheme 5, Table 1 (entries 1–5)]. Under standard conditions, alkylated derivatives **16a–d** were obtained from primary alkyl halides in good yields, varying from 67% to near-quantitative. These yields refer to characterized materials isolated by flash chromatography. A representative secondary alkyl halide, 2-bromopropane, failed to react with deprotonated **3**. Diastereomeric ratios were calculated on crude product mixtures immediately after work-up, being estimated from ^{13}C NMR spectral peak intensities and verified in most cases by GC–MS. Disappointingly, the asymmetric induction at the new chiral centre was virtually nil in all cases.

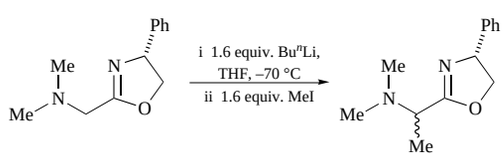


3

16a R = Me
b R = Et
c R = Bn
d R = allyl

Scheme 5

A number of control reactions were performed in an effort to explain the absence of stereochemical control. In the first instance, the possibility of epimerization due to an excess of base was ruled out: treatment of **3** with 0.95 equiv. of Bu^{n}Li followed by iodoethane simply gave **16b** in reduced yield with no improvement in the diastereomeric ratio (entry 6). In order to assess the importance of the steric bulk of the benzyl groups borne by **3**, the dimethyl analogue **15** was alkylated with iodomethane under the same conditions (Scheme 6). The prod-



15 **17**

Scheme 6

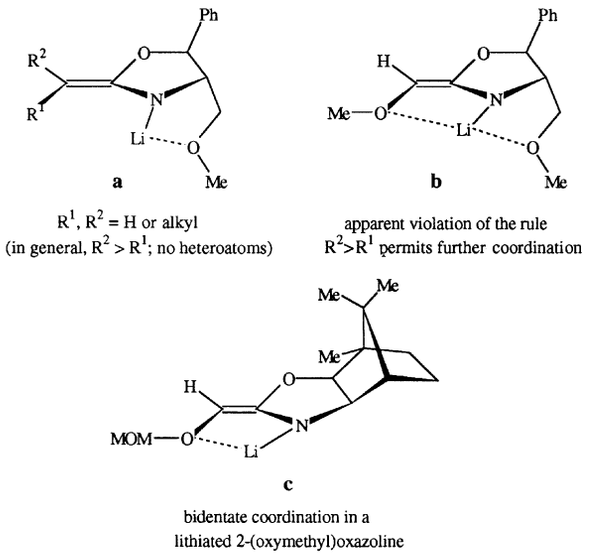
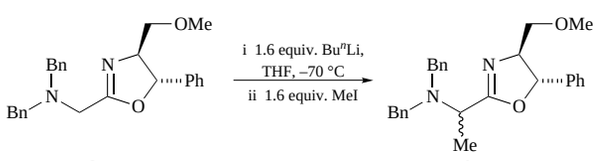


Fig. 2

uct **17** was obtained in satisfactory yield but with no asymmetric induction at the new chiral centre (entry 7).

We were concerned that (*R*)-phenylglycinol might have been an inappropriate choice of chiral adjuvant. In particular, we were aware that Meyers[1] had invoked a key role for the *C*4 methoxymethyl substituent in the complexation of the lithium ion by the metallated intermediate during the alkylation of carbon-chain *C*2 substituted oxazolines (Fig. 2, a). However, in the alkylation of his 2-(methoxymethyl)oxazoline, Meyers[4] observed a stereochemical induction consistent with lithium complexation by the *C*2 substituent's methoxy group (Fig. 2, **b**), while Kelly and Arvanitis[5] obtained good stereochemical induction during the alkylation of a 2-(methoxymethyl)-oxazoline in which the heterocycle was derived from camphor and had no other functionality capable of complexing a lithium ion (Fig. 2, **c**). Thus, the presence of a complexing function at *C*4 (or *C*5) does not seem to be a prerequisite for asymmetric induction in the alkylation of a heteroatom-bearing carbon substituent at *C*2. Nonetheless, we decided to test the reactivity of the Meyers-type aminooxazoline **13**. In the event, alkylation with iodomethane under standard conditions (Scheme 7) gave



13 **18**

Scheme 7

the expected product **18**, but once again the diastereomeric excess was very low (Table 1, entry 8).

Some explanation was sought for the lack of stereochemical induction. For the successful asymmetric alkylation of a prochiral methylene group such as that in **3**, selective reaction of the electrophile with one face of a rigid enolate-type intermediate **19** is required (Fig. 3). The bulk of the phenyl substituent should favour reaction from the opposite side of the oxazolidine ring plane. The metallated intermediate can often be stabilized *via* complexation of the metal ion by heteroatomic functions, as illustrated by Fig. 2. A crucial point, however, first shown in 1978 by Hoobler *et al.*[27] and Meyers *et al.*[28] for metallated 2-alkyloxazolines, is that the *Z* and *E* intermediates are not in equilibrium. We assume the same principle to apply here for amino derivatives. Thus, in the alkylation of **3**, the stereochemistry of the product **16** will be determined by the relative

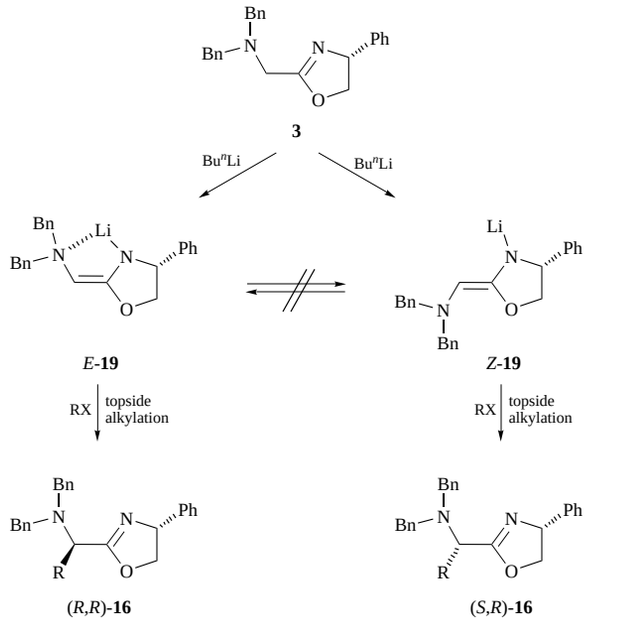


Fig. 3

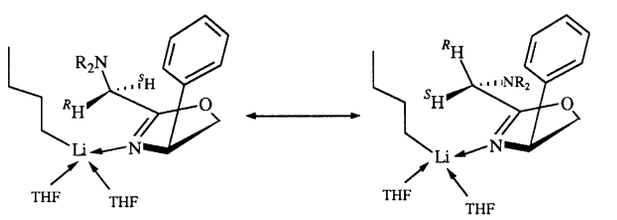


Fig. 4 Monodentate nitrogen ligation and intramolecular deprotonation is possible

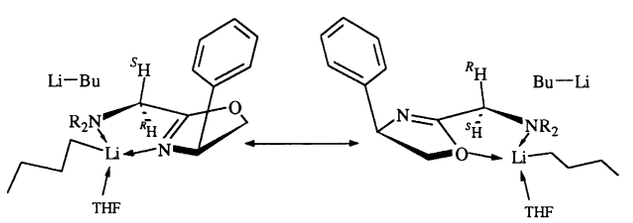


Fig. 5 Non-discriminate bidentate coordination and intermolecular deprotonation is necessary

ease of formation of *Z* and *E* enolates **19**, not the relative stability of the structures; there is no guarantee that the attractive bidentate system *E*-**19** will predominate. Here, we can only speculate on the precise nature of the molecular interactions leading up to deprotonation; however, two plausible systems should be considered.

In the first instance, we consider the monodentate ligation of a molecule of Bu^{n}Li by the oxazoline nitrogen of **3** (Fig. 4). Subsequent 'intramolecular' (strictly speaking, 'intracomplex') elimination of a butane molecule is non-selective, however, since the free rotation of the *C*2–*C*1′ bond allows non-discriminate removal of either the pro-*R* hydrogen, leading to *E*-**19**, or the pro-*S* hydrogen, giving *Z*-**19**. Likewise, the involvement of a second molecule of base to deprotonate the monodentate Bu^{n}Li·**3** complex seems unlikely to be stereoselective. An alternative possibility for the initial interaction is the formation of a bidentate Bu^{n}Li·**3** complex (Fig. 5). It is not easy to predict whether an *N*,*N* or an *N*,*O* lithium ligand system is preferred, although these systems give opposite dispositions of the pro-*S* and pro-*R* hydrogens. Furthermore, in either case, 'intramolecular' elimination of butane is disfavoured because

Table 2 Alkylation of tertiary carbamate oxazoline **7**[a]

Entry	Equiv. Bu^{n}Li	Electrophile	Product	Yield (%)[b]	Diastereomeric ratio[c]
1	1.0	MeI	**20a**	30[d]	88:12
2		EtI	**20b**	33[d]	96:4
3		$PhCH_2Br$	**20c**	18[d]	95:5
4		PrI	**20e**	20[d]	92:8
5	1.6	MeI	**20a**	61 (90)[e]	73:27
6		EtI	**20b**	52	71:29
7		Pr^{i}Br	—	—[f]	—
8	2.0	MeI	**20a**	44	80:20
9		EtI	**20b**	56	73:27
10		$PhCH_2Br$	**20c**	46	70:30
11		allyl Br	**20d**	47	n.d.[g]

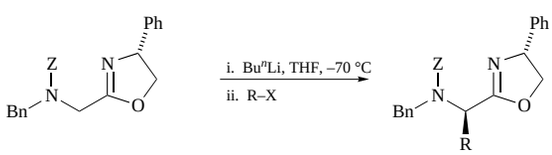
[a] See text for standard conditions. [b] Isolated yields after chromatography are quoted. [c] Determined on crude reaction mixtures immediately after work up; estimated error ±3%. [d] Unreacted starting material was also recovered (20–40%). [e] The yield in parentheses is for almost pure product before chromatography. [f] Only unreacted starting material was recovered (93% before chromatography). [g] Not determined; diastereomers were not separated on analytical systems.

the butyl group and the methylene protons represent 1,3-disposed substituents, oriented away from each other, on a five-membered ring system. An external molecule of base is therefore necessary to effect deprotonation. Stereochemical control in this system, then, is fraught with difficulties: the 'intermolecular' deprotonation may not be stereoselective (implying preferred approach towards one side of the oxazoline ring), and even if this were the case, the initial complex might not be structurally homogeneous.

Although we have not obtained further experimental evidence, it is interesting to note that the above arguments, in addition to highlighting the problems of stereochemical control, may go some way towards explaining the apparent need for a moderate excess of base in order to achieve efficient deprotonation of **3**. In any event, it is clear that tertiary amine oxazolines do not allow the same degree of asymmetric induction as has been observed for other systems.

Alkylation of tertiary carbamate derivatives

We turned our attention to the deprotonation–alkylation reactivity of the carbamate system **7** (Scheme 8), for which



7

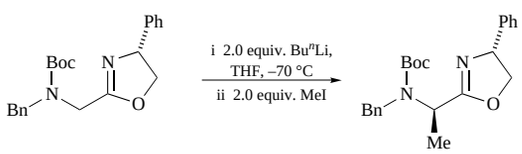
20a R = Me
b R = Et
c R = Bn
d R = allyl
e R = Pr

Scheme 8

results are summarized in Table 2. As with the tertiary amine **3**, deprotonation was not very efficient with one equivalent of Bu^{n}Li at −70 °C, but it was possible to obtain alkylated derivatives **20** in up to 33% yield after addition of simple primary electrophiles (entries 1–4). The figures shown are for pure compounds obtained after flash chromatography, and it was evident that some loss of material occurred during this operation, presumably through degradation.‡ Such a procedure was, however, necessary, since the alkylation products **20** were accompanied by unreacted starting material **7**. From NMR and HPLC analysis of the crude product mixtures, we estimate that the actual yields of the reaction may be around 40–50% each for **20** and starting material. The salient feature in these reactions was the diastereomeric ratio for the new products, estimated by HPLC or GC–MS analysis of the product mixtures immediately after work up. The lowest diastereomeric ratio was a reasonable 88:12, obtained for the methyl derivative, and all others were better than 90:10.

Several efforts were made to improve the yields, but the figures shown in Table 2 were the best that we were able to reproduce using only one equivalent of base. For entries 1 and 2, alkylation was attempted using LDA or Bu^{s}Li instead of Bu^{n}Li, but resulted in near-zero yields of **20a** and **20b**. Similarly, the use of additives such as TMEDA, HMPA or LiCl suppressed formation of the alkylation products. For entry 2, longer (8 h) or more forcing (0 °C) metallation conditions before addition of the electrophile made no difference to the results. The only way to improve the yields was to use an excess of base to effect deprotonation. When 1.6 equiv. (entries 5 and 6) or 2.0 equiv. (entries 8–11) of Bu^{n}Li were used, products **20** were obtained in yields varying from 44–61%; again, these figures are for isolated materials and we estimate that the actual yields in crude reaction products may be considerably higher. No unreacted starting material was observed, and the crude materials were relatively pure, being accompanied by unreacted excess electrophile as the only other main component. Indeed, for entry 5, the crude reaction product (after removal of all volatiles) was virtually pure by NMR spectroscopy, and represented a yield of 90%. Diastereomeric ratios were still fairly reasonable, ranging from 70:30 upwards, although they were in general lower than those for the corresponding alkylation reactions carried out with only one equivalent of base. As with the tertiary amine **3**, the alkylation of **7** failed when a secondary alkyl halide was used as the electrophile (entry 7).

One reaction was carried out on the Boc-carbamate **10** (Scheme 9). Metallation with 2.0 equiv. of Bu^{n}Li followed by

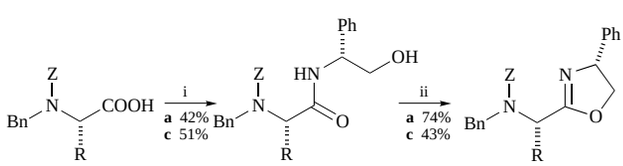


10 **21**

Scheme 9

treatment with iodomethane gave the expected product **21** with a yield (48%) and a diastereomeric ratio (80:20) comparable with the analogous reaction giving **20a** from **7** (Table 2, entry 8).

The absolute stereochemistry of the major diastereomer of each product **20** was expected to be *R* as shown in Scheme 8 (*vide infra*) and this was proven for the two compounds **20a** and **20c** by HPLC comparison with authentic samples prepared independently as follows (Scheme 10). The (*S*)-alanine derivative **22a** was condensed with (*R*)-phenylglycinol to give amide



22 **23** **20**

a R = Me
c R = Bn

Scheme 10 *Reagents and conditions:* i, Bu^{i}OCOCl, *N*-methylmorpholine, THF, −15 °C, then (*R*)-phenylglycinol; ii, $Et_3\overset{+}{N}SO_2\bar{N}COOMe$, THF, reflux

‡ Langlois and co-workers (ref. 11) made the same observation concerning the sensitivity of their (aminomethyl)oxazolines.

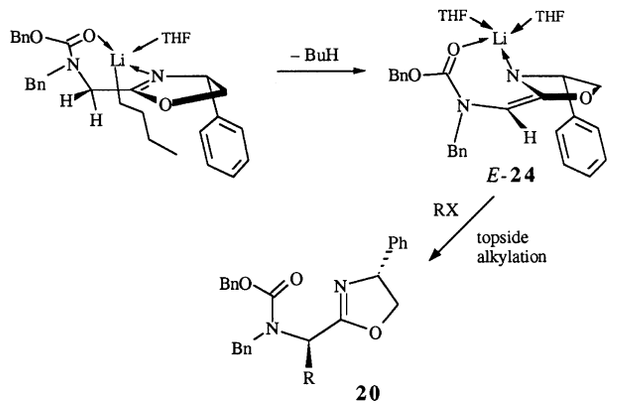


Fig. 6 Possible origin of stereoselectivity in alkylation of tertiary carbamates

23a. Cyclodehydration with Burgess' salt gave authentic **20a**, enriched in the (4*R*,1′*S*)-isomer.§ In a similar fashion, (4*R*,1′*S*)-enriched **20c** was obtained *via* **23c** from the (*S*)-phenylalanine derivative **22c**.

The much improved stereochemical induction obtained with the tertiary carbamates can be explained by a consideration of the initial interaction between base and substrate, again on the assumption that intermediate enolate structures cannot equilibrate. Complexation of the carbamate oxygen and the ring nitrogen of **7** to the lithium atom gives a seven-membered chelate structure (Fig. 6). Examination of simple models of this Bu^{n}Li·**7** adduct suggest no strain in the system, and the only transannular interaction is between the pseudo-axial *n*-butyl group and one of the *C*1′ protons. This situation may be favourable for the elimination of *n*-butane to produce only the *E*-**24** enolate. Models suggest that the bottomside of *E*-**24** is blocked not only by the *C*4 phenyl substituent, as expected, but also to a certain extent by the benzyl group of the exocyclic nitrogen. Topside alkylation should therefore predominate, leading preferentially to an *R* absolute configuration at the alkylated centre.

Concluding remarks

Although the 2-(aminomethyl)oxazolines studied here require care in their manipulation, they can be alkylated in a manner similar to that shown previously for 2-alkyloxazolines. Tertiary amine derivatives give good chemical yields, but the poor diastereomeric excesses in the products suggest little potential use in asymmetric synthesis. Tertiary carbamate derivatives present a more useful system, since asymmetric induction is much better. Future exploitation of this type of compound in synthesis will depend on whether alkylation is successful with more elaborate electrophiles, and whether the problem of material loss can be avoided. With respect to this latter point, it is worth recalling that the crude reaction products obtained from Scheme 8, in which 1.6 or 2.0 equiv. of base are used, are relatively clean (estimated purity *ca.* 90% by NMR spectroscopy and HPLC) and represent chemical yields upwards of 60–70%. Depending on the subsequent use intended for compounds such as **20**, this may conceivably be practical for synthetic purposes.

Experimental

General

Mps were determined on a Kofler hot stage and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300.13 and 75.43 MHz respectively on a Bruker AC 300-P instrument. Chemical shifts are given in ppm with reference to $SiMe_4$ and observed coupling constants *J* are given in Hz. IR Spectra were recorded on a Perkin-Elmer FTIR 1600 spectrometer as solutions in either dichloromethane or chloroform unless otherwise indicated. Optical rotations were obtained using a Perkin-Elmer 141 polarimeter and $[\alpha]_D$ values are expressed in units 10^{-1} deg cm^2 g^{-1}. Chemical ionization mass spectra (CIMS) were recorded on a Nermag R10-10 instrument at 30 eV using ammonia as the ionizing gas. High resolution mass spectra were recorded on a Kratos MS-80 instrument operating in chemical ionization mode at 70 eV using methane as the ionizing gas. Elemental analyses were performed by Service de Microanalyse, Institut de Chimie des Substances Naturelles du CNRS, Gif-sur-Yvette, France. Analytical TLC was performed on silica gel F-254 plates of 0.2 mm thickness and components visualized using UV light then stained using ethanolic phosphomolybdic acid solution. R_f Values are given for the same solvent system as was used for flash chromatography. Flash chromatography was carried out on 230–400 mesh silica gel. For all compounds containing an oxazoline function, the silica gel was previously dried overnight at 120 °C and the elution solvents were previously dried over $MgSO_4$. Tetrahydrofuran was distilled immediately prior to use from sodium benzophenone ketyl. Dichloromethane, triethylamine and diisopropylamine were distilled from calcium hydride prior to use. Alkyl halides were passed through a short plug of basic alumina, except benzyl bromide, which was distilled immediately before use. Commercial solutions of butyllithium in hexane were titrated regularly according to two different procedures, using *N*-pivaloyl-*o*-toluidine[29] or diphenylacetic acid[30] as the indicator, and were used only when calculated concentrations agreed to within 5%. All other commercial reagents and solvents were used as supplied. Compounds **1**,[21] **4**,[21] **12**,[4] **14**,[26] **22a**[31] and **22c**[31] are described in the literature. Diastereomeric ratios were determined by GC–MS analysis (Varian 3400 instrument with a DB-5 column, Finnigan INCOS 50 spectrometer) or by HPLC analysis (Waters 660 instrument, Novapac column, eluent EtOAc–heptane 15:85).

(*R*)-*N*-(*N*,*N*-Dibenzylglycyl)phenylglycinol 2

N-Methylmorpholine (4.22 ml, 38.4 mmol) and isobutyl chloroformate (4.57 ml, 35.2 mmol) were added to a solution of *N*,*N*-dibenzylglycine **1** (10.61 g, 41.6 mmol) in THF (500 ml) at −15 °C. After stirring for 45 min, a solution of (*R*)-phenylglycinol (4.39 g, 32.0 mmol) in THF (25 ml) was added *via* cannula. The temperature was allowed to rise to 20 °C over 3 h, then the mixture was filtered and the precipitate washed with EtOAc. The filtrate was evaporated under reduced pressure. Flash chromatography of the residue using EtOAc–cyclohexane (50:50) as eluent gave the title compound **2** as a white solid (10.53 g, 88%), mp 110 °C (EtOAc–light petroleum) (Found: C, 77.14; H, 6.96; N, 7.55. $C_{24}H_{26}N_2O_2$ requires C, 76.97; H, 6.99; N, 7.48%); R_f 0.27; $[\alpha]_D^{24}$ −7.9 (*c* 1.03, $CHCl_3$); ν_{max}/cm^{-1} 3367br, 1658; δ_H($CDCl_3$) 2.77 (1H, br s, OH), 3.19 (2H, m, CH_2), 3.67 (4H, m, 2 × CH_2Ph), 3.80 (2H, m, CH_2O), 4.91 (1H, dt, *J* 7.1 and 5.0, C*H*Ph), 7.15–7.38 (15H, m, Ph), 7.90 (1H, d, *J* 7.1, NH); δ_C($CDCl_3$) 56.1 (*C*HPh), 57.5 (CH_2), 59.6 (CH_2Ph), 67.1 (CH_2O), 126.8, 127.7, 128.0, 128.7, 129.0 and 129.1 (CH_{ar}), 138.0 and 138.9 (C_{ar}), 171.8 (CO); *m/z* (CIMS) 375 $[MH]^+$.

(*R*)-2-(Dibenzylamino)methyl-4-phenyl-4,5-dihydrooxazole 3

A solution of amide **2** (5.24 g, 14.0 mmol) and triphenylphosphine (4.41 g, 16.8 mmol) in THF (70 ml) was stirred at 0 °C under nitrogen for 45 min. Diethyl azodicarboxylate (2.65 ml, 16.8 mmol) was then added dropwise and the solution stirred at room temp. for 3 h. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography using EtOAc–cyclohexane (20:80) as eluent to give

§ Burgess' salt is reported to be non-racemizing (ref. 23), in contrast with other cyclodehydrating agents. In our experiments, partial (but not complete) racemization was observed, leading to diastereomeric mixtures. This was in fact useful for our purposes, since it allowed visualization of both stereoisomers in the analytical systems used, but would clearly have presented a problem if stereochemically pure samples had been required.

the title compound **3** as a clear oil (2.74 g, 55%) which solidified slowly on standing, mp 61 °C (Found: C, 80.81; H, 6.87; N, 7.80. $C_{24}H_{24}N_2O$ requires C, 80.87; H, 6.79; N, 7.89%); R_f 0.24; $[\alpha]_D^{24}$ +48.2 (*c* 1.08, $CHCl_3$); ν_{max}/cm^{-1} 1655; $\delta_H(CDCl_3)$ 3.46 (2H, s, CH_2), 3.81 (4H, s, 2 × CH_2Ph), 4.09 (1H, t, *J* 8.6, CH_2O), 4.58 (1H, dd, *J* 10.0 and 8.6, CH_2O), 5.17 (1H, dd, *J* 10.0 and 8.1, CH), 7.21–7.46 (15H, m, Ph); $\delta_C(CDCl_3)$ 49.6 (CH_2), 58.0 (CH_2Ph), 69.7 (CH), 74.5 (CH_2O), 126.8, 127.1, 127.6, 128.3, 128.7 and 129.0 (CH_{ar}), 138.9 and 142.3 (C_{ar}), 166.2 (CN); *m/z* (CIMS) 357 $[MH]^+$.

***N*-Benzyl-*N*-(benzyloxycarbonyl)glycine 5**

Sodium hydrogen carbonate (3.36 g, 40.1 mmol) was added to an ice-cold solution of *N*-benzylglycine hydrochloride **4** (2.02 g, 10.0 mmol) in water (47 ml) and the mixture stirred until complete dissolution was achieved. Benzyl chloroformate (1.8 ml, 12.6 mmol) was then added and the resulting mixture was allowed to warm to room temp. After 3 h the solution was acidified to pH 4 with 1 M HCl then extracted with EtOAc (3 × 30 ml). The combined extracts were dried over $MgSO_4$ and then evaporated to dryness to give the title compound **5** as a colourless oil (2.84 g, 95%) (Found: C, 68.02; H, 5.82; N, 4.33. $C_{17}H_{17}NO_4$ requires C, 68.22; H, 5.68; N, 4.68%); ν_{max}/cm^{-1} 3650–2400, 1701; $\delta_H(CDCl_3)$ 3.93 and 4.01 (2H, 2s, CH_2 rotamers), 4.58 and 4.61 (2H, 2s, CH_2Ph rotamers), 5.19 and 5.22 (2H, 2s, OCH_2Ph rotamers), 7.15–7.41 (10H, m, Ph), 9.65 (1H, br s, COOH); $\delta_C(CDCl_3)$ 47.1 and 47.9 (CH_2 rotamers), 51.4 (CH_2Ph), 68.1 (OCH_2Ph), 127.6, 127.7, 127.9, 128.1, 128.4 and 128.6 (CH_{ar}), 136.2 and 136.6 (C_{ar}), 156.4 and 156.9 (NCOO rotamers), 174.7 (COOH); *m/z* (CIMS) 300 $[MH]^+$, 317 $[MH + NH_3]^+$.

(*R*)-*N*-[*N*-Benzyl-*N*-(benzyloxycarbonyl)glycyl]phenylglycinol 6

Following the procedure used for the synthesis of compound **2**, a solution of protected amino acid **5** (2.93 g, 9.8 mmol) in THF (100 ml) was treated with *N*-methylmorpholine (1.34 ml, 12.2 mmol) and isobutyl chloroformate (1.21 ml, 9.3 mmol) followed by (*R*)-phenylglycinol (1.34 g, 9.8 mmol) in THF (25 ml). The title compound **6** was obtained without chromatography as a white solid (3.21 g, 78%), mp 147 °C (EtOAc–light petroleum) (Found: C, 71.67; H, 6.40; N, 6.62. $C_{25}H_{26}N_2O_4$ requires C, 71.75; H, 6.26; N, 6.69%); R_f 0.24 (EtOAc–cyclohexane 40:60); $[\alpha]_D^{24}$ −14.2 (*c* 1.10, $CHCl_3$); ν_{max}/cm^{-1} 3473, 3310, 1694, 1652; $\delta_H(CDCl_3)$ 2.75 (1H, br s, OH), 3.55–3.80 (2H, m, CH_2O), 3.91 (2H, br s, CH_2), 4.61 (2H, br s, CH_2Ph), 4.85–5.06 (1H, m, CH), 5.20 (2H, br s, OCH_2Ph), 6.92–7.12 (1H, br s, NH), 7.18–7.41 (15H, m, Ph); $\delta_C(CDCl_3)$ 50.6 and 50.9 (CH_2 rotamers), 52.1 and 52.4 (CH_2Ph rotamers), 55.6 (CH), 66.0 (CH_2O), 68.0 (OCH_2Ph), 126.6, 127.8, 128.1, 128.3, 128.6 and 128.8 (CH_{ar}), 136.1, 136.8 and 138.8 (C_{ar}), 156.5 and 157.0 (NCOO rotamers), 169.3 (CO); *m/z* (CIMS) 419 $[MH]^+$.

(*R*)-2-[Benzyl(benzyloxycarbonyl)amino]methyl-4-phenyl-4,5-dihydrooxazole 7

A suspension of amide **6** (1.59 g, 3.8 mmol) and Burgess' salt (1.00 g, 4.2 mmol) in THF (80 ml) was refluxed for 24 h. The solvent was evaporated under reduced pressure and the residue was taken up in EtOAc–cyclohexane (50:50) and filtered through a short plug of silica. Evaporation of the filtrate gave the title compound **7** as a colourless oil (1.33 g, 87%) (Found: MH^+, 401.1877. $C_{25}H_{24}N_2O_3$ requires MH^+, 401.1865); R_f 0.41; $[\alpha]_D^{24}$ +38.2 (*c* 0.91, $CHCl_3$); ν_{max}/cm^{-1} 1703, 1672sh; $\delta_H(CDCl_3)$ 4.02 (1H, m, CH*H*O), 4.15 and 4.28 (2H, 2s, CH_2 rotamers), 4.56 (1H, m, C*H*HO), 4.67 (2H, s, CH_2Ph), 5.12 (1H, m, CH), 5.21 (2H, s, OCH_2Ph), 7.02–7.36 (15H, m, Ph); $\delta_C(CDCl_3)$ 43.1 and 43.6 (CH_2 rotamers), 50.9 and 51.3 (CH_2Ph rotamers), 67.7 (OCH_2Ph), 69.6 (CH), 75.0 (CH_2O), 126.6, 127.6, 128.0, 128.2, 128.5 and 128.7 (CH_{ar}), 136.5, 137.1 and 141.8 (C_{ar}), 156.4 (NCOO), 164.8 (CN).

***N*-Benzyl-*N*-(*tert*-butoxycarbonyl)glycine 8**

Sodium hydroxide (0.39 g, 9.7 mmol) was added to a stirred solution of *N*-benzylglycine hydrochloride **4** (0.50 g, 2.4 mmol) in a mixture of water (7 ml) and dioxane (7 ml). After complete dissolution had been achieved, di-*tert*-butyl dicarbonate (0.59 g, 2.7 mmol) was added and the resulting solution stirred at room temp. for 48 h. After concentration to half volume, the residual solution was acidified to pH 3–4 with 1 M HCl and extracted with dichloromethane (3 × 15 ml). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure to give the title compound **8** as a white solid (0.49 g, 75%), mp 107 °C (cyclohexane) (Found: C, 63.28; H, 7.28; N, 5.36. $C_{14}H_{19}NO_4$ requires C, 63.38; H, 7.22; N, 5.28%); ν_{max}/cm^{-1} 3600–2400, 1729, 1699; $\delta_H(CDCl_3)$ 1.49 (9H, s, 3 × CH_3), 3.82 and 3.94 (2H, 2s, CH_2 rotamers), 4.50 and 4.55 (2H, 2s, CH_2Ph rotamers), 7.20–7.40 (5H, m, Ph), 9.30 (1H, br s, COOH); $\delta_C(CDCl_3)$ 28.2 (CH_3), 47.6 (CH_2), 51.5 and 50.8 (CH_2Ph rotamers), 80.9 and 81.1 (CMe_3 rotamers), 127.5, 128.1 and 128.6 (CH_{ar}), 137.4 (C_{ar}), 156.0 (NCOO), 175.2 and 175.7 (COOH rotamers); *m/z* (CIMS) 266 $[MH]^+$, 283 $[MH + NH_3]^+$.

(*R*)-*N*-[*N*-Benzyl-*N*-(*tert*-butoxycarbonyl)glycyl]phenylglycinol 9

Following the procedure used for the synthesis of compound **2**, a solution of protected amino acid **8** (1.43 g, 5.4 mmol) in THF (20 ml) was treated with *N*-methylmorpholine (0.67 ml, 6.2 mmol) and isobutyl chloroformate (0.67 ml, 5.1 mmol) followed by (*R*)-phenylglycinol (0.74 g, 5.4 mmol) in THF (5 ml). Flash chromatography using EtOAc–cyclohexane (40:60) as eluent gave the title compound **9** as a white solid (1.87 g, 90%), mp 91 °C (diethyl ether) (Found: C, 68.79; H, 7.30; N, 7.35. $C_{22}H_{28}N_2O_4$ requires C, 68.73; H, 7.34; N, 7.29%); R_f 0.19; $[\alpha]_D^{20}$ −17.5 (*c* 1.01, $CHCl_3$); ν_{max}/cm^{-1} 3425, 3320, 1693, 1667; $\delta_H(CDCl_3)$ 1.37 (9H, s, 3 × CH_3), 3.07 (1H, br s, OH), 3.60 and 3.70 (4H, 2s, CH_2 and CH_2OH), 4.41 (2H, br s, CH_2Ph), 4.88 (1H, m, CH), 6.42, 6.87 and 7.04 (1H, 3m, NH), 7.09–7.28 (10H, m, Ph); $\delta_C(CDCl_3)$ 28.1 (CH_3), 51.0 (CH_2), 52.3 (CH_2Ph), 55.4 (CH), 65.9 (CH_2O), 81.2 (CMe_3), 126.6, 127.6 and 128.6 (CH_{ar}), 137.2 and 138.7 (C_{ar}), 156.0 (NCOO), 169.8 (COOH); *m/z* (CIMS) 385 $[MH]^+$.

(*R*)-2-[Benzyl(*tert*-butoxycarbonyl)amino]methyl-4-phenyl-4,5-dihydrooxazole 10

A suspension of amide **9** (0.40 g, 1.0 mmol) and Burgess' salt (0.27 g, 1.1 mmol) in THF (20 ml) was refluxed for 24 h. The solvent was evaporated under reduced pressure and the residue was taken up in EtOAc–cyclohexane (50:50) and filtered through a short plug of silica. Evaporation of the filtrate gave the title compound **10** as a colourless oil (0.28 g, 73%) (Found: MH^+, 367.2023. $C_{22}H_{26}N_2O_3$ requires MH^+, 367.2022); R_f 0.75; $[\alpha]_D^{20}$ +37.9 (*c* 0.62, CH_2Cl_2); ν_{max}/cm^{-1} 1693, 1665sh; $\delta_H(CDCl_3)$ 1.49 and 1.51 (9H, 2s, 3 × CH_3), 4.02–4.18 (3H, m, CH_2 and CH*H*O), 4.55 (3H, m, CH_2Ph and C*H*HO), 5.15 (1H, dd, *J* 9.2 and 8.9, C*H*Ph), 7.18–7.34 (10H, m, Ph); $\delta_C(CDCl_3)$ 28.2 (CH_3), 42.9 and 43.1 (CH_2 rotamers), 50.3 and 50.9 (CH_2Ph rotamers), 69.4 (*C*HPh), 74.8 and 74.9 (CH_2O rotamers), 80.3 and 80.5 (CMe_3 rotamers), 126.5, 127.2, 127.4, 128.0, 128.4 and 128.5 (CH_{ar}), 137.5 and 141,9 (C_{ar}), 155.5 (CO), 165.1 (CN).

(4*S*,5*S*)-2-(Dibenzylamino)methyl-4-methoxymethyl-5-phenyl-4,5-dihydrooxazole 13

Triethylamine (0.13 ml, 0.94 mmol) was added to a solution of (chloromethyl)oxazoline **12** (188 mg, 0.78 mmol) and dibenzylamine (0.18 ml, 0.94 mmol) in DMF (15 ml) and the resulting mixture was stirred at room temp. for 2 days. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography using EtOAc–cyclohexane (30–70) as eluent to give the title compound **13** as a colourless oil (123 mg, 39%) (Found: MH^+, 401.2247. $C_{26}H_{28}N_2O_2$ requires MH^+, 401.2229); R_f 0.23; $[\alpha]_D^{25}$ −4.7 (*c* 0.78, $CHCl_3$);

ν_{max}/cm^{-1} 1661; δ_H($CDCl_3$) 3.40 (3H, s, OCH_3), 3.41 (1H, d, *J* 14.7, C*H*H), 3.45 (1H, d, *J* 14.7, CH*H*), 3.49 (1H, dd, *J* 6.3 and 9.6, CH*H*OMe), 3.63 (1H, dd, *J* 4.2 and 9.6, C*H*HOMe), 3.74 (2H, d, *J* 13.6, CH_2Ph), 3.83 (2H, d, *J* 13.6, CH_2Ph), 4.15 (1H, m, NCH), 5.33 (1H, d, *J* 6.7, OC*H*Ph), 7.21–7.43 (15H, m, Ph); δ_C($CDCl_3$) 49.6 (CH_2), 57.7 (*C*H_2Ph), 59.2 (OCH_3), 74.2 (NCH and *C*H_2OMe), 83.2 (O*C*HPh), 125.5, 127.0, 128.0, 128.2, 128.6 and 128.8 (CH_{ar}), 138.8 and 140.2 (C_{ar}), 165.6 (CN).

(*R*)-2-(Dimethylamino)methyl-4-phenyl-4,5-dihydrooxazole 15

Triethylamine (1.75 ml, 12.2 mmol) was added dropwise to a solution of (*R*)-phenylglycinol (0.72 g, 5.3 mmol) and methyl (dimethylamino)iminoacetate dihydrochloride **14** (1.02 g, 5.4 mmol) in dichloromethane (40 ml) and the resulting mixture was stirred at room temp. overnight. The solvent was evaporated and the residue was taken up in diethyl ether and THF and then filtered. After evaporation of the filtrate, flash chromatography of the residue using EtOAc–MeOH–NH_4OH (90:9:1) as eluent gave the title compound **15** as a colourless oil (80 mg, 7%); R_f 0.32; ν_{max}/cm^{-1} 1664; δ_H($CDCl_3$) 2.40 (6H, s, 2 × CH_3), 3.29 (2H, s, CH_2), 4.15 (1H, t, *J* 8.5, CH*H*O), 4.66 (1H, dd, *J* 8.6 and 10.1, C*H*HO), 5.22 (1H, t, *J* 9.3, C*H*Ph), 7.24–7.37 (5H, m, Ph); δ_C($CDCl_3$) 45.5 (CH_3), 55.9 (CH_2), 69.5 (CH), 74.5 (CH_2O), 126.4, 127.4 and 128.6 (CH_{ar}), 141.9 (C_{ar}), 165.6 (CN); *m/z* (CIMS) 205 $[MH]^+$.

General procedure for the preparation of oxazolines 16, 17, 18, 20 and 21

A solution of *n*-butyllithium in hexane (containing 0.60, 0.96 or 1.20 mmol, depending on the number of equivalents of base required; see Tables 1 and 2 for details) was added dropwise to a solution of oxazoline **3**, **7**, **10**, **13** or **15** (0.60 mmol) in THF (10 ml) at −70 °C under a nitrogen atmosphere. After 15 min, the alkyl halide (0.60, 0.96 or 1.20 mmol; neat) was added dropwise. After a further 3 h at −70 °C, the reaction mixture was treated with saturated aqueous NH_4Cl (10 ml) and then warmed to room temp. The resulting mixture was extracted with dichloromethane (3 × 10 ml) and the combined extracts were dried over $MgSO_4$ then evaporated. Flash chromatography of the residue using EtOAc–cyclohexane (20:80) as eluent gave the following compounds as colourless or pale yellow oils (see Tables 1 and 2 for diastereomeric compositions).

(4*R*,1′*RS*)-2-[1′-(Dibenzylamino)ethyl]-4-phenyl-4,5-dihydrooxazole 16a. Obtained in 92% yield from oxazoline **3** and 1.6 equiv. of *n*-butyllithium using iodomethane as the alkyl halide (Found: MH^+, 371.2121. $C_{25}H_{26}N_2O$ requires MH^+, 371.2123); R_f 0.30; ν_{max}/cm^{-1} 1650; δ_H($CDCl_3$) 1.41 and 1.42 (3H, 2d, each *J* 7.0, CH_3), 3.75–3.82 (5H, m, C*H* and 2 × CH_2Ph), 4.12 (1H, m, CH*H*O), 4.61 (1H, m, C*H*HO), 5.19 (1H, m, C*H*Ph), 7.15–7.45 (15H, m, Ph); δ_C($CDCl_3$) 15.2 (CH_3), 51.4 (CH), 54.4 (*C*H_2Ph), 69.4 and 69.6 (*C*HPh), 74.2 (CH_2O), 126.5, 126.6, 126.8, 127.4, 128.1 and 128.6 (CH_{ar}), 139.9 and 142.4 (C_{ar}), 168.9 and 169.1 (CN).

(4*R*,1′*RS*)-2-[1′-(Dibenzylamino)propyl]-4-phenyl-4,5-dihydrooxazole 16b. Obtained in 67% yield from oxazoline **3** and 1.6 equiv. of *n*-butyllithium using iodoethane as the alkyl halide (Found: MH^+, 385.2281. $C_{26}H_{28}N_2O$ requires MH^+, 385.2280); R_f 0.37; ν_{max}/cm^{-1} 1650; δ_H($CDCl_3$) 0.95 (3H, t, *J* 7.3, CH_3), 1.86 (2H, m, CH_2), 3.43 (1H, m, CH), 3.65 (2H, d, *J* 14.1, 2 × CH*H*Ph), 3.99 (2H, d, *J* 14.1, 2 × C*H*HPh), 4.12 (1H, dd, *J* 1.8 and 8.3, C*H*HO), 4.64 (1H, dd, *J* 1.8 and 8.3, CH*H*O), 5.26 (1H, t, *J* 8.3, C*H*Ph), 7.18–7.56 (15H, m, Ph); δ_C($CDCl_3$) 11.2 (CH_3), 23.3 (CH_2), 54.6 (*C*H_2Ph), 57.6 (CH), 69.5 and 69.7 (*C*HPh), 73.9 (CH_2O), 126.7, 126.8, 127.4, 128.1, 128.6 and 128.8 (CH_{ar}), 139.9 and 142.5 (C_{ar}), 167.8 (CN).

(4*R*,1′*RS*)-2-(1′-Dibenzylamino-2′-phenylethyl)-4-phenyl-4,5-dihydrooxazole 16c. Obtained in 71% yield from oxazoline **3** and 1.6 equiv. of *n*-butyllithium using benzyl bromide as the alkyl halide (Found: MH^+, 447.2429. $C_{31}H_{30}N_2O$ requires MH^+, 447.2436); R_f 0.38; ν_{max}/cm^{-1} 1651; δ_H($CDCl_3$) 3.18 (2H, m, CH_2), 3.61–3.72 (2H, m, 2 × CH*H*Ph), 3.88–4.10 (4H, m, 2 × C*H*HPh, CH, CH*H*O), 4.57 (1H, m, C*H*HO), 5.18 (1H, m, C*H*Ph), 7.02–7.41 (20H, m, Ph); δ_C($CDCl_3$) 36.1 and 36.4 (CH_2), 54.5 and 54.6 (*C*H_2Ph), 57.2 and 57.7 (CH), 69.5 and 69.6 (*C*HPh), 74.1 and 74.2 (CH_2O), 126.1, 126.7, 126.8, 127.4, 128.1, 128.7 and 129.5 (CH_{ar}), 138.4, 139.4 and 142.3 (C_{ar}), 166.9 (CN).

(4*R*,1′*RS*)-2-[1′-(Dibenzylamino)but-3′-enyl]-4-phenyl-4,5-dihydrooxazole 16d. Obtained in 95% yield from oxazoline **3** and 1.6 equiv. of *n*-butyllithium using allyl bromide as the alkyl halide (Found: MH^+, 397.2285. $C_{27}H_{28}N_2O$ requires MH^+, 397.2280); R_f 0.40; ν_{max}/cm^{-1} 1651; δ_H($CDCl_3$) 2.64 (2H, t, *J* 6.7, CH_2), 3.58–3.67 (3H, m, C*H* and 2 × CH*H*Ph), 3.94 (2H, d, *J* 13.8, 2 × C*H*HPh), 4.09 and 4.11 (1H, 2t, each *J* 8.3, CH*H*O), 4.61 and 4.62 (1H, 2t, each *J* 8.3, C*H*HO), 5.02–5.10 (2H, m, =CH_2), 5.24 (1H, m, C*H*Ph), 5.74–5.88 (1H, m, =CH), 7.19–7.41 (15H, m, Ph); δ_C($CDCl_3$) 34.6 (CH_2), 54.5 (*C*H_2Ph), 55.9 and 56.0 (CH), 69.5 and 69.7 (*C*HPh), 74.1 (CH_2O), 116.7 (=CH_2), 126.6, 126.9, 127.5, 128.1, 128.7 and 128.9 (CH_{ar}), 135.4 (=CH), 139.7 and 142.4 (C_{ar}), 167.3 and 167.4 (CN).

(4*R*,1′*RS*)-2-[1′-(Dimethylamino)ethyl]-4-phenyl-4,5-dihydrooxazole 17. Obtained in 47% yield from oxazoline **15** and 1.6 equiv. of *n*-butyllithium using iodomethane as the alkyl halide and EtOAc–MeOH–NH_4OH (90:9:1) as the flash chromatography eluent (Found: MH^+, 219.1492. $C_{13}H_{18}N_2O$ requires MH^+, 219.1497); R_f 0.38; ν_{max}/cm^{-1} 1653; δ_H($CDCl_3$) 1.39 and 1.40 (3H, 2d, each *J* 6.9, CH_3), 2.39 (6H, s, 2 × NCH_3), 3.48 and 3.49 (1H, 2q, each *J* 6.9, CH), 4.11 and 4.14 (1H, 2t, each *J* 8.4, CH*H*O), 4.65 and 4.66 (1H, 2dd, each *J* 10.3 and 8.5, C*H*HO), 5.22 (1H, t, *J* 8.8, C*H*Ph), 7.23–7.37 (5H, m, Ph); δ_C($CDCl_3$) 14.4 and 14.5 (CH_3), 41.6 (NCH_3), 58.1 (CH), 69.1 (*C*HPh), 74.8 (CH_2O), 126.5, 127.6 and 128.7 (CH_{ar}), 141.7 (C_{ar}), 167.9 (CN).

(4*S*,5*S*,1′*RS*)-2-[1′-(Dibenzylamino)ethyl]-4-methoxymethyl-5-phenyl-4,5-dihydrooxazole 18. Obtained in 65% yield from oxazoline **13** and 1.6 equiv. of *n*-butyllithium using iodomethane as the alkyl halide and EtOAc–cyclohexane (40:60) as the flash chromatography eluent (Found: MH^+, 415.2380. $C_{27}H_{30}N_2O_2$ requires MH^+, 415.2385); R_f 0.34; ν_{max}/cm^{-1} 1648; δ_H($CDCl_3$) 1.43 and 1.44 (3H, 2d, each *J* 7.0, CH_3), 3.42 and 3.43 (3H, 2s, OCH_3), 3.47–3.54 (1H, m, CH), 3.64–3.75 (2H, m, CH_2OMe), 3.73 (2H, d, *J* 13.6, 2 × C*H*HPh), 3.83 (2H, d, *J* 13.6, 2 × CH*H*Ph), 4.17 (1H, m, NCH), 5.35 and 5.40 (1H, 2d, each *J* 6.7, OC*H*Ph), 7.18–7.46 (15H, m, Ph); δ_C($CDCl_3$) 14.4 and 15.0 (CH_3), 51.4 and 51.5 (CH), 54.3 (*C*H_2Ph), 58.4 (OCH_3), 69.1 (NCH), 71.9 (*C*H_2OMe), 82.7 (O*C*HPh), 126.4, 126.8, 127.7, 127.9, 128.1 and 128.6 (CH_{ar}), 136.4 and 139.9 (C_{ar}), 168.4 and 168.8 (CN).

(4*R*,1′*R*)-2-{1′-[Benzyl(benzyloxycarbonyl)amino]ethyl}-4-phenyl-4,5-dihydrooxazole 20a. Obtained in 30% yield from oxazoline **7** and 1.0 equiv. of *n*-butyllithium using iodomethane as the alkyl halide (Found: MH^+, 415.2029. $C_{26}H_{26}N_2O_3$ requires MH^+, 415.2022); R_f 0.11; ν_{max}/cm^{-1} 1694, 1661; δ_H($CDCl_3$) 1.49 (3H, m, CH_3), 3.87 (1H, m, CH), 4.46–4.68 (3H, m, CH_2Ph and CH*H*O), 5.06–5.32 (4H, m, C*H*HO, C*H*Ph, OCH_2Ph), 7.05–7.49 (15H, m, Ph); δ_C($CDCl_3$) 16.2 (CH_3), 47.8 (*C*H_2Ph), 49.8 (CH), 67.4 (O*C*H_2Ph), 69.6 (*C*HPh), 74.8 (CH_2O), 125.8, 126.7, 127.4, 127.8, 128.2 and 128.6 (CH_{ar}), 136.3, 138.4 and 141.6 (C_{ar}), 156.4 (CO), 167.6 (CN).

(4*R*,1′*R*)-2-{1′-[Benzyl(benzyloxycarbonyl)amino]propyl}-4-phenyl-4,5-dihydrooxazole 20b. Obtained in 33% yield from oxazoline **7** and 1.0 equiv. of *n*-butyllithium using iodoethane as the alkyl halide (Found: MH^+, 429.2171. $C_{27}H_{28}N_2O_3$ requires MH^+, 429.2178); R_f 0.18; ν_{max}/cm^{-1} 1694, 1655; δ_H($CDCl_3$) 0.94 (3H, m, CH_3), 1.30–1.92 (2H, m, CH_2), 3.78 (1H, t, *J* 8.5, CH), 4.33–4.81 (4H, m, CH_2O, CH_2Ph), 4.96–5.28 (3H, m, C*H*Ph, OCH_2Ph), 7.02–7.39 (15H, m, Ph); δ_C($CDCl_3$) 10.7 (CH_3), 23.4 (CH_2), 47.3 (CH), 55.3 (*C*H_2Ph), 67.7 (O*C*H_2Ph), 69.7 (*C*HPh), 74.6 (CH_2O), 126.4, 126.7, 126.9,

127.4, 127.8, 128.0, 128.2 and 128.5 (CH_{ar}), 136.6, 138.3 and 141.4 (C_{ar}), 156.8 (CO), 166.7 (CN).

(4*R*,1′*R*)-2-[1′-Benzyl(benzyloxycarbonyl)amino-2′-phenylethyl]-4-phenyl-4,5-dihydrooxazole 20c. Obtained in 18% yield from oxazoline **7** and 1.0 equiv. of *n*-butyllithium using benzyl bromide as the alkyl halide (Found: MH^+, 491.2342. $C_{32}H_{30}N_2O_3$ requires MH^+, 491.2335); R_f 0.21; ν_{max}/cm^{-1} 1697, 1660; $\delta_H(CDCl_3)$ 3.10–3.46 (2H, m, CH_2), 3.62–3.88 (1H, m, CH), 4.28–4.81 and 4.89–5.31 (7H, 2m, CH_2O, CH_2Ph, C*H*Ph, OCH_2Ph), 7.02–7.45 (20H, m, Ph); $\delta_C(CDCl_3)$ 36.2 and 36.7 (CH_2 rotamers), 48.5 and 48.9 (*C*H_2Ph rotamers), 55.3 (CH), 67.5 (O*C*H_2Ph), 69.7 (*C*HPh), 74.6 (CH_2O), 126.5, 126.7, 126.8, 127.4, 128.1, 128.2, 128.4, 128.5, 128.7 and 129.2 (CH_{ar}), 136.3, 137.1 and 141.4 (C_{ar}), 156.3 (CO), 166.1 (CN).

(4*R*,1′*R*)-2-{1′-[Benzyl(benzyloxycarbonyl)amino]but-3′-enyl}-4-phenyl-4,5-dihydrooxazole 20d. Obtained in 47% yield from oxazoline **7** and 2.0 equiv. of *n*-butyllithium using allyl bromide as the alkyl halide (Found: MH^+, 441.2182. $C_{28}H_{28}N_2O_3$ requires MH^+, 441.2178); R_f 0.20; ν_{max}/cm^{-1} 1700, 1654; $\delta_H(CDCl_3)$ 2.58–2.83 (2H, m, CH_2), 3.72 (1H, m, CH), 4.28–4.80 (4H, m, CH_2O, CH_2Ph), 4.89–5.54 (5H, m, =CH_2, C*H*Ph, OCH_2Ph), 5.54–5.92 (1H, m, =CH), 7.03–7.51 (15H, m, Ph); $\delta_C(CDCl_3)$ 34.4 (CH_2), 47.5 (*C*H_2Ph), 53.5 (CH), 67.5 and 67.7 (O*C*H_2Ph rotamers), 69.2 and 69.6 (*C*HPh rotamers), 74.4 (CH_2O), 118.0 (=CH_2), 126.3, 126.6, 127.4, 128.0, 128.1, 128.2 and 128.4 (CH_{ar}), 133.5 (=CH), 136.1, 138.0 and 141.2 (C_{ar}), 156.6 (CO), 166.2 (CN).

(4*R*,1′*R*)-2-{1′-[Benzyl(benzyloxycarbonyl)amino]butyl}-4-phenyl-4,5-dihydrooxazole 20e. Obtained in 20% yield from oxazoline **7** and 1.0 equiv. of *n*-butyllithium using iodopropane as the alkyl halide (Found: MH^+, 443.2343. $C_{28}H_{30}N_2O_3$ requires MH^+, 443.2335); R_f 0.22; ν_{max}/cm^{-1} 1695, 1660; $\delta_H(CDCl_3)$ 0.72–0.89 (3H, m, CH_3), 1.17–1.41 (2H, m, CH_2), 1.77–2.05 (2H, m, CH_2), 3.78 (1H, t, *J* 8.5, CH), 4.37–4.58 (1H, m, CH*H*O), 4.58 (2H, br s, CH_2Ph), 4.98–5.31 (4H, m, C*H*HO, C*H*Ph, OCH_2Ph), 7.03–7.44 (15H, m, Ph); $\delta_C(CDCl_3)$ 13.6 (CH_3), 19.3 (CH_2), 32.1 (CH_2), 47.3 (*C*H_2Ph), 53.6 (CH), 67.6 (O*C*H_2Ph), 69.7 (*C*HPh), 74.5 (CH_2O), 126.7, 127.5, 127.8, 128.2, 128.3 and 128.6 (CH_{ar}), 136.6, 138.3 and 142.0 (C_{ar}), 156.9 (CO), 166.9 (CN).

(4*R*,1′*R*)-2-{1′-[Benzyl(*tert*-butoxycarbonyl)amino]ethyl}-4-phenyl-4,5-dihydrooxazole 21. Obtained in 48% yield from oxazoline **10** and 2.0 equiv. of *n*-butyllithium using iodomethane as the alkyl halide (Found: MH^+, 381.2171. $C_{23}H_{28}N_2O_3$ requires MH^+, 381.2178); R_f 0.26; ν_{max}/cm^{-1} 1686, 1663sh; $\delta_H(CDCl_3)$ 1.29–1.48 (12H, m, 4 × CH_3), 3.88 (1H, t, *J* 8.6, CH*H*O), 4.35–4.62 (4H, m, C*H*HO, CH_2Ph, C*H*), 5.12 (1H, t, *J* 8.6, C*H*Ph), 7.10–7.35 (10H, m, Ph); $\delta_C(CDCl_3)$ 16.4 (CH_3), 28.3 (Boc-CH_3), 47.6 (*C*H_2Ph), 48.9 (CH), 69.7 (*C*HPh), 74.7 and 74.8 (CH_2O rotamers), 80.4 (*C*Me_3), 126.5, 126.7, 127.5, 128.2, 128.6 and 128.7 (CH_{ar}), 139.4 (C_{ar}), 141.8 and 142.1 (C_{ar} rotamers), 155.6 (CO), 168.2 (CN).

(*R*)-*N*-(*N*-Benzyl-*N*-benzyloxycarbonyl-L-alanyl)phenylglycinol 23a

Following the procedure used for the synthesis of compound **2**, a solution of protected amino acid **22a** (0.65 g, 2.1 mmol) in THF (25 ml) was treated with *N*-methylmorpholine (0.26 ml, 2.4 mmol) and isobutyl chloroformate (0.25 ml, 1.9 mmol) followed by (*R*)-phenylglycinol (0.28 g, 2.0 mmol). Flash chromatography using EtOAc–cyclohexane (50:50) gave the title compound **23a** as a white solid (0.37 g, 42%), mp 126 °C (EtOAc–light petroleum bp 35–60 °C) (Found: C, 71.72; H, 6.61; N, 6.51. $C_{26}H_{28}N_2O_4$ requires C, 72.18; H, 6.52; N, 6.48%); R_f 0.24; $[\alpha]_D^{17}$ −58.1 (*c* 1.19, $CHCl_3$); ν_{max}/cm^{-1} 3420, 1694, 1682; $\delta_H(CDCl_3)$ 1.91 (3H, d, *J* 8.0, CH_3), 3.18 (1H, br s, OH), 3.42–3.81 (2H, m, CH_2O), 4.19–4.40 (1H, m, CH), 4.50–4.70 (2H, br s, CH_2Ph), 4.80–5.02 (1H, m, C*H*Ph), 5.15 (2H, br s, OCH_2Ph), 6.25 (1H, br s, NH), 6.90–7.38 (15H, m, Ph); $\delta_C(CDCl_3)$ 14.4 (CH_3), 49.3 (*C*H_2Ph), 55.5 (CH), 56.1 (*C*HPh), 66.0 (CH_2OH), 67.8 (O*C*H_2Ph), 126.5, 127.0, 127.4, 127.8, 128.0, 128.3 and 128.5 (CH_{ar}), 135.8, 138.1 and 138.9 (C_{ar}), 159.9 (NCOO), 171.4 (CO); *m/z* (CIMS) 433 $[MH]^+$.

(*R*)-*N*-(*N*-Benzyl-*N*-benzyloxycarbonyl-L-phenylalanyl)phenylglycinol 23c

Following the procedure used for the synthesis of compound **2**, a solution of protected amino acid **22c** (2.27 g, 5.8 mmol) in THF (50 ml) was treated with *N*-methylmorpholine (0.73 ml, 6.7 mmol) and isobutyl chloroformate (0.72 ml, 5.6 mmol) followed by (*R*)-phenylglycinol (0.80 g, 5.8 mmol). Flash chromatography using EtOAc–cyclohexane (30:70) as eluent gave the title compound **23c** as a white solid (1.50 g, 51%), mp 105 °C (EtOAc–light petroleum) (Found: C, 75.11; H, 6.38; N, 5.51. $C_{32}H_{32}N_2O_4$ requires C, 75.56; H, 6.34; N, 5.51%); R_f 0.29; $[\alpha]_D^{17}$ −33.3 (*c* 0.66, MeOH); ν_{max}(Nujol)/cm^{-1} 3283, 3228, 1694, 1644; $\delta_H(CD_3OD)$ 2.99–3.25 (2H, m, CH_2Ph), 3.50–3.78 (2H, m, CH_2OH), 4.08–4.12 (1H, m, CH), 4.73–4.91 (3H, m, NCH_2Ph and NC*H*Ph), 5.22 (2H, s, OCH_2Ph), 6.18 (1H, br s, NH), 7.15–7.53 (20H, m, Ph); $\delta_C(CD_3OD)$ 36.4 (CH_2), 50.9 and 51.9 (*C*H_2Ph), 56.7 and 63.2 (CH and *C*HPh), 65.7 (CH_2O), 68.7 (O*C*H_2Ph), 127.6, 127.7, 128.1, 128.5, 129.3, 129.5 and 130.3 (CH_{ar}), 137.5, 138.6, 139.4 and 140.6 (C_{ar}), 157.8 (CO), 171.6 (CO); *m/z* (CIMS) 509 $[MH]^+$.

Dehydrocyclization of amide 23a

Following the procedure used for the synthesis of compound **7**, amide **23a** (0.31 g, 0.71 mmol), was treated with Burgess' salt (0.18 g, 0.78 mmol) to give oxazoline **(4*R*,1′*S*)-20a** (0.22 g, 74%). Partial epimerization to the (4*R*,1′*R*)-isomer was evidenced by HPLC analysis.

Dehydrocyclization of amide 23c

Following the procedure used for the synthesis of compound **7**, amide **23c** (0.20 g, 0.39 mmol) was treated with Burgess' salt (0.10 g, 0.43 mmol). Flash chromatography of the crude product using EtOAc–cyclohexane (20:80) as eluent gave oxazoline **(4*R*,1′*S*)-20c** (82 mg, 43%). Partial epimerization to the (4*R*,1′*R*)-isomer was evidenced by HPLC analysis.

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