FEATURE ARTICLE

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Addition reactions of ROPHy/SOPHy oxime ethers: asymmetric synthesis of nitrogen containing compounds

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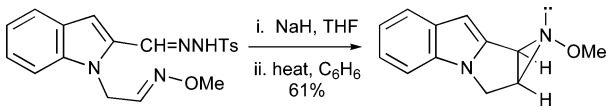
Oxime ethers prepared from (*R*)- or (*S*)-*O*-(1-phenylbutyl)hydroxylamine (ROPHy or SOPHy) are versatile intermediates for the asymmetric synthesis of a range of nitrogen containing compounds including simple amines, 1,2-aminoalcohols, α- and β-amino acids, heterocyclic building blocks of natural products, piperidine alkaloids, lactams, 5- to 8-membered ring nitrogen heterocycles, imino-sugars, and chiral ferrocene based receptors.

Introduction

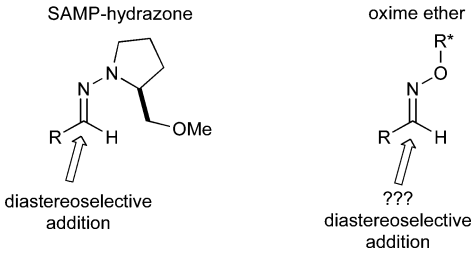
Amines and their derivatives bearing a chiral centre at the α-position play a fundamental part in life processes. Even relatively simple amines, amino alcohols and amino acids occupy vital roles as hormones, neurotransmitters, building blocks *etc.*, and the structurally more complex alkaloids, the most diverse class of natural products, exhibit a wide range of biological activity. In addition, nitrogen containing molecules find increasing use in asymmetric synthesis as chiral ligands and auxiliaries.

In the late 1980s, my research group was looking to develop new methods for the asymmetric synthesis of biologically active saturated nitrogen heterocycles to complement our work on 'flat-earth' heterocyclic compounds, and in an approach to the tetracyclic ring structure of the mitomycins, we investigated the formation of fused aziridines. This resulted in the first example of a formal intramolecular cycloaddition of a carbene to the C=N bond of an oxime ether, and gave the desired *N*-alkoxy aziridine in good yield (Scheme 1).[1,2]



Scheme 1

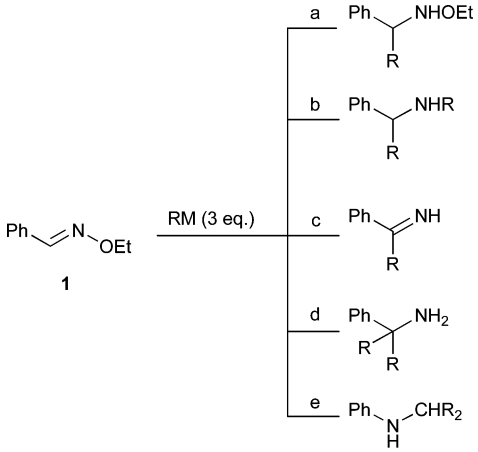
The above success immediately raised the question as to whether we could develop an asymmetric version of the above cycloaddition reaction by using a chiral oxime ether, and, indeed, could such chiral oxime ethers also undergo other potentially useful transformations such as the addition of carbon nucleophiles? However, in comparison to the well known asymmetric addition reactions of aldehydes and ketones, the corresponding reactions of C=N bonds had been much less well studied. In part, the development of such reactions had been limited by the poor electrophilicity of the C=N carbon, as well as the tendency of compounds with α-protons to undergo deprotonation rather than addition with organometallic reagents. Nowadays, asymmetric addition to a range of C=N bonds (imines, hydrazones, sulfinimines, nitrones, *etc.*) is well known,[3–8] but at the time (early 1990s), one of the best known examples of such a process involved the (*R*)- and (*S*)-1-amino-2-(methoxymethyl)pyrrolidine (RAMP and SAMP) derived hydrazones developed by Enders.[9] Oxime ethers, despite their potential, had found relatively little use in asymmetric synthesis, and therefore we wondered whether it was possible to develop chemistry of chiral oxime ethers that might parallel that of Enders' hydrazones (Scheme 2, R* = chiral group). This Feature Article describes the results of a decade of our work in this area, which has resulted in the successful development of ROPHy/SOPHy oxime ethers, named by analogy with RAMP/SAMP hydrazones, as useful intermediates in asymmetric synthesis.



Scheme 2

Background

Although this Article is not intended as a comprehensive review, some introductory remarks on the addition reactions of oxime ethers are required. An early report appeared in 1907 when Busch and Hobein described the addition of phenylmagnesium bromide to *O*-methyl benzaldoxime.[10] Not only did the Grignard reagent add to the C=N bond, but the intermediate underwent a further addition to give, with displacement of methoxide, the secondary amine $Ph_2CHNHPh$. Many years later the addition of *n*-butyllithium to *O*-butyl cyclohexanone oxime was reported to give the corresponding hydroxylamine without addition of a second molecule of the organometallic.[11] The unpredictable nature of such reactions was confirmed in a detailed study by Pornet and Migniac in the mid-1970s who found that addition of an organometallic reagent RM (3 equiv.) to *O*-ethylbenzaldoxime **1** could give rise to a range of products (Scheme 3).[12] Thus, depending on the conditions and the



Scheme 3

organometallic reagent used, the reaction resulted in (a) the expected addition product — the hydroxylamine, (b) the double addition product resulting from loss of ethoxide, (c) initial elimination of ethoxide to give a nitrile followed by addition to give an imine (or its ketone hydrolysis product), (d) addition of the

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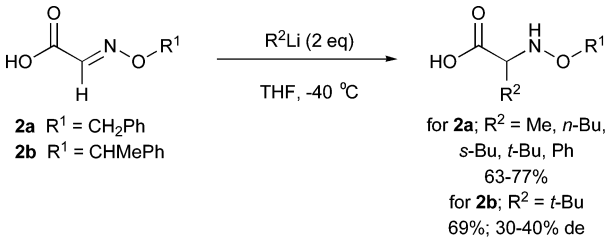
organometallic reagent to the imine, or (e) Beckmann rearrangement derived products. Although, subsequently, the double addition reactions have been exploited in synthesis, *O*-benzyl formaldoxime acting as a [$^{+}CH_2NH^{+}$] synthon,[13] the addition of organometallic reagents to oxime ethers is clearly not a simple process!

From the earlier accounts it seemed evident that some activation of the oxime ether towards nucleophilic attack, would be necessary if high yields of the simple addition products, the hydroxylamines, were to be obtained. Thus, Miller investigated the reactions of the *O*-benzyl oxime of glyoxylic acid **2a** in which the electrophilicity of the C=N bond is increased by the electron withdrawing carboxylate, and which gave high yields of the required hydroxylamines (Scheme 4).[14] Importantly, in the context of this Feature

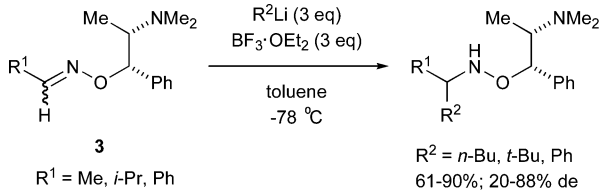


Scheme 4

Article, Miller also described the use of a chiral auxiliary, the *O*-(1-phenylethyl) oxime ether **2b**, and observed modest diastereoselectivity in the addition of *tert*-butyllithium (Scheme 4).

In the same paper,[14] Miller also reported the use of chiral glyoxylamides, and again observed modest diastereoselectivity (20–47% de) in the formation of the hydroxylamines upon addition of alkyllithiums. In related work, the *O*-methyl oxime derived from the chiral glyoxylate ester of 8-phenylmenthol was investigated, and found to undergo addition of allyl-zinc and — boron reagents in poor to excellent diastereoselectivity (6–> 98% de).[15] In a similar more recent study, the *O*-benzyl oxime of the glyoxylamide derived from Oppolzer's camphorsultam gave good to excellent diastereoselectivity (62–98% de) when reacted with allylzinc reagents,[16] and there are a number of other examples involving additions to oxime ethers bearing a chiral auxiliary on the *carbon* atom of the oxime C=N bond.[15,17,18]

Although the use of oxime ethers derived from glyoxylic acid derivatives was moderately successful in that good yields of the required hydroxylamines were generally obtained without any of the previously observed complications (*cf.* Scheme 3), a more general method was needed. Following earlier reports on the use of trimethylsilyl triflate to mediate the addition of ketene silyl acetals to *O*-benzyl formaldoxime,[19] and of the addition of penicillin derived Grignard reagents to *O*-ethyl formaldoxime and *O*-methyl acetaldoxime in the presence of boron trifluoride diethyl etherate,[20] a detailed study on the addition of aryllithium reagents to oxime ethers in the presence of Lewis acids was undertaken by Rodriques *et al.*[21] Boron trifluoride diethyl etherate proved to be the most effective Lewis acid and mediated the addition of organolithiums to *O*-benzyl acetaldoxime at low temperature in THF, although it was suggested that only the Z-isomer of the oxime reacted efficiently. In later work, Uno *et al.* extended the range of organolithium additions to oxime ethers in the presence of $BF_3{\cdot}OEt_2$, obtaining higher yields by switching to toluene, suggesting that the success of the reaction depended on coordination of the boron trifluoride to the nitrogen of the C=N bond free from competition by coordinating solvents such as THF.[22] Although it appeared after we had started our own work (see below), a key paper in this area was the 1993 contribution from Dieter and Datar which reported the first detailed study of oxime ethers bearing a chiral auxiliary attached to oxygen.[23] Thus the *N*-methylephedrine derived oxime ethers **3** underwent addition of organolithiums in toluene at low temperature in the presence of $BF_3{\cdot}OEt_2$ to give the corresponding hydroxylamines in good yield with up to 88% de (Scheme 5). Hence it was with this background that we embarked upon our own studies of oxime ethers bearing a chiral auxiliary on oxygen.[24]



Scheme 5

Early results

In attempting (1991) to design oxime ethers in which one diastereotopic face of the C=N bond is sterically shielded, we made some general assumptions about their conformations, in particular the almost planar nature of the C=N–O fragment and the *trans*-arrangement around the N–O bond. Such assumptions were supported by X-ray studies of oxime derivatives in the solid state, and therefore we considered simple chiral ethers of *anti*-aldoximes such as **4** in which a large group R^1 shields one face of the C=N–O plane. Such structures were, of course, analogous to the *O*-(1-phenylethyl) glyoxylic acid derived oximes studied by Miller,[14] and although the reported diastereoselectivities of their addition reactions were modest, we considered further studies were justified. We also considered oxime ethers **5** in which it was proposed that the intramolecular hydrogen bond would impart extra rigidity to the structure (Fig. 1). Finally, by analogy with previous studies on

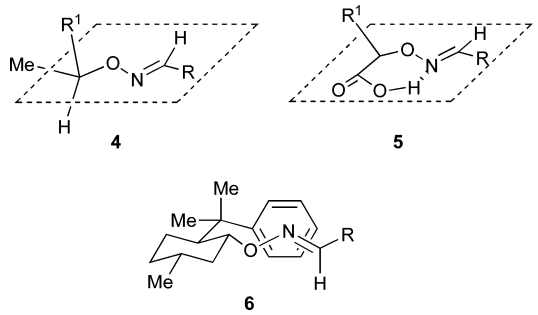
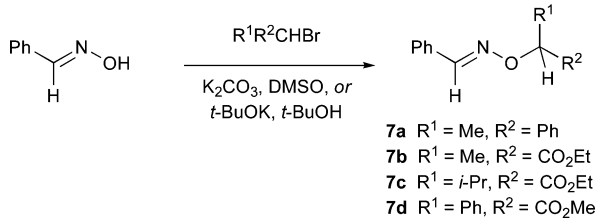


Fig. 1 Early ideas for chiral oxime ethers.

oximes with a chiral auxiliary attached to the carbon atom of the C=N–O fragment,[15] we also considered the 8-phenylmenthol derived (*E*)-aldoxime ethers **6** (Fig. 1).

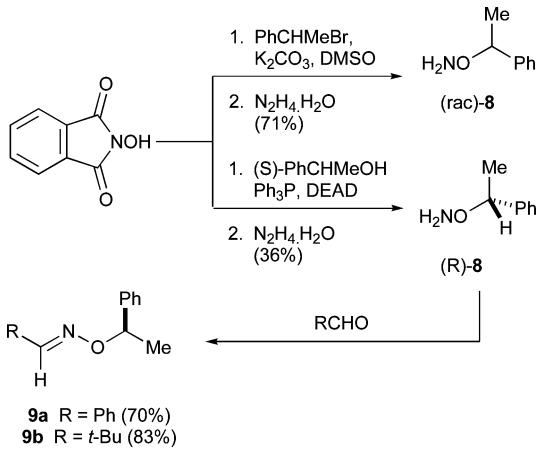
Two routes were envisaged for the preparation of such oxime ethers: (i) the alkylation of the corresponding oxime RCH=NOH, or (ii) by reaction of an aldehyde RCHO with the chiral hydroxylamine R^*ONH_2, itself potentially available by amination of a readily available chiral alcohol R*OH, or by alkylation of a compound such as *N*-hydroxyphthalimide in which the N–O bond is already formed, followed by removal of the *N*-protecting group. The first route looked straightforward, and therefore I asked Elizabeth Swann, a postdoc in the group, to do some preliminary experiments to check whether such oxime ethers could be made. Liz soon found that benzaldoxime could be alkylated with α-methylbenzyl bromide and with α-bromoesters to give oxime ethers **7** in racemic form (Scheme 6). The ester group in **7d** was hydrolysed to the corresponding crystalline acid **5** (R = R^1 = Ph), subsequent X-ray analysis of which showed, unfortunately, that it did not adopt our proposed H-bonded conformation (Fig. 1).

Armed with the above knowledge, our first grant was submitted and funded under the Link Asymmetric Synthesis Programme, a joint UK government-industry initiative. Hence with support from our industrial partner Lilly Research, the first PhD, Andrew Lightfoot, student started work on the project in October 1993. Our



Scheme 6

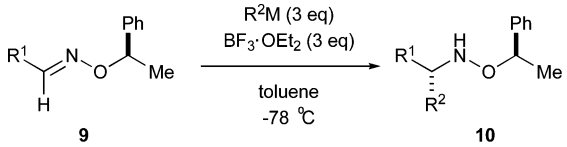
original intentions had been to study the cycloaddition reactions of the C=N as a potential Diels–Alder route to chiral piperidines, or as a carbene route to chiral aziridines (*cf.* Scheme 1); in the event we started with the addition of organometallic reagents to the C=N bond. Andy quickly discovered that addition of *n*-butyllithium to carboxylate containing oximes (*e.g.* **7b–7d**) resulted in attack on the C=O rather than the C=N bond. He also found that our projected route to chiral hydroxylamines by amination of secondary alcohols, readily available from the chiral pool, using chloramine was an unsatisfactory process despite literature precedent,[25] and, although Choong and Ellman have recently reported improved conditions for this transformation,[26] at the time Andy focused on relatively simple oxime ethers such as the α-phenylethyl derivatives **4** (R^1 = Ph) and **7a**. The racemic hydroxylamine **8** was easily prepared by alkylation of *N*-hydroxyphthalimide, followed by standard hydrazine cleavage of the phthaloyl group. Hydroxylamine **8** could also be prepared as a single enantiomer by Mitsunobu reaction of *N*-hydroxyphthalimide with (*S*)-(−)-1-phenethyl alcohol which gave, after cleavage of the phthaloyl group, the (*R*)-(+)-hydroxylamine **8** in 36% yield and in > 95% enantiomeric excess as judged by ^{1}H NMR spectroscopy in the presence of Eu(hfc)$_3$. Reaction of the (*R*)-hydroxylamine **8** with benzaldehyde and pivaldehyde gave the corresponding oxime ethers **9** exclusively as the (*E*)-isomers in good yield (Scheme 7).[27,28]



Scheme 7

Although our initial attempts to effect addition of organometallic reagents to the oxime ethers **9** were disappointing, adoption of conditions reported by Dieter and Datar, whose paper had just appeared,[23] proved highly satisfactory. These conditions which involved the dropwise addition of the organometallic reagent (3 equiv.) to a mixture of the oxime ether substrate and $BF_3{\cdot}OEt_2$ (3 equiv.) in toluene at −78 °C became our standard protocol for subsequent work. The use of THF as solvent is particularly deleterious, presumably because it competes with the weakly Lewis basic oxime ether for the boron trifluoride (see below). Other Lewis acids proved largely unsatisfactory. The yield of hydroxylamines **10** obtained from these first addition reactions were variable (21–84%), but some of the diastereomeric excesses, readily determined from their ^{1}H NMR spectra, were extremely satisfying (38–95% de). The results are summarised in Table 1, with the stereochemistry of the major diastereomer resulting from the

Table 1 Addition of organometallic reagents to *O*-(1-phenylethyl) aldoximes **9**



9 **10**

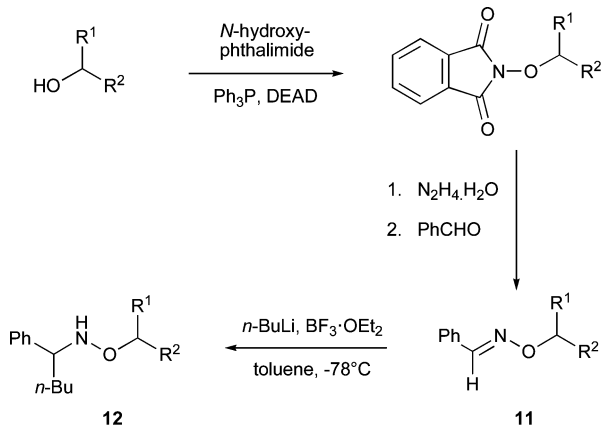
Entry	R^1	R^2M	**10** Yield (%)	**10** de (%)
1	Ph	*n*-BuLi	64	71
2	Ph	*t*-BuLi	54	38
3	Ph	$H_2C{=}CHCH_2MgBr$	70	69
4	Ph	*i*-PrMgCl	30	74
5	*t*-Bu	*n*-BuLi	84	74
6	*t*-Bu	$H_2C{=}CHCH_2MgBr$	62	44
7	*t*-Bu	PhLi	21	95

1,4-asymmetric induction shown. The stereochemical outcome of the addition was proved in two ways. Firstly the hydrochloride of hydroxylamine **10** (R^1 = Ph, R^2 = allyl) formed crystals suitable for X-ray analysis, and secondly the N–O bond in hydroxylamine **10** (R^1 = Ph, R^2 = *n*-Bu) was cleaved using zinc/acetic acid/ultrasound to give the known (*R*)-1-phenylpentylamine.[27,28]

Although diastereomeric excesses of 95% could be achieved using the simple *O*-(1-phenylethyl) oximes **9**, more routinely the de was in the range 60–80% (Table 1), and therefore an auxiliary which was more effective than the α-methylbenzyl group in controlling the 1,4-asymmetric induction was sought.

Development of (*R*)- and (*S*)-*O*-(1-phenylbutyl)hydroxylamine; ROPHy/SOPHy oxime ethers

A series of simple benzaldoxime ethers **11** containing α-arylalkyl groups as chiral auxiliaries was readily prepared in racemic form from the corresponding secondary alcohol by Mitsunobu reaction with *N*-hydroxyphthalimide, hydrazine cleavage of the phthaloyl group and condensation with benzaldehyde (Scheme 8).[29] The



Scheme 8

effectiveness of the auxiliaries was ascertained in the addition of *n*-butyllithium to the oxime ethers under our standard conditions to give the corresponding hydroxylamines in varying de (Table 2). Initially we had thought that the α-naphthylethyl auxiliary with the bulkier aryl group might prove more effective than its phenyl counterpart, but in the event resulted in somewhat poorer diastereoselectivity (55 *vs.* 71% de). However, increasing the size of the alkyl group had the desired effect, and the α-phenylalkyl auxiliaries (Table 2, Entries 3–6) performed well. In contrast, the oxime ether derived from 2-butanol gave very poor de (~10%) in the addition of *n*-butyllithium. The best results were obtained with

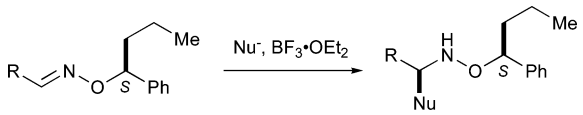
Table 2 Addition of *n*-butyllithium to *O*-(1-arylalkyl) benzaldoximes **11**

Entry	R^1	R^2	**12** Yield (%)	**12** de (%)
1	Me	Ph	64	71
2	Me	1-Naphthyl	80	55
3	Et	Ph	91	93
4	*n*-Pr	Ph	87	90
5	*i*-Pr	Ph	74	> 95
6	*n*-Bu	Ph	80	90

the auxiliary derived from 2-methyl-1-phenylpropanol (Entry 5), although the fact that its Mitsunobu reaction proceeded in poor yield (32%) coupled with its unavailability as single enantiomers from suppliers, led us to select the α-phenylbutyl auxiliary for further study. The starting alcohol, 1-phenylbutanol, was commercially available as both enantiomers and was readily converted into the corresponding hydroxylamines, (*R*)- and (*S*)-*O*-(1-phenylbutyl)hydroxylamines, both > 96% ee as determined by ^{1}H NMR spectroscopy in the presence of TFAE. The hydroxylamines were subsequently named ROPHy/SOPHy by Andy Lightfoot, and have been used in a wide range of transformations in our laboratory over the last decade.

Origin of the diastereoselectivity

In most cases the levels of 1,4-asymmetric induction observed in the addition reactions of ROPHy/SOPHy derived oxime ethers are excellent, and the stereochemical outcome is highly predictable, the incoming nucleophile adding from the side occupied by the alkyl group. Hence if the incoming group Nu has a lower priority in the Sequence Rules than the existing group R, the new stereocentre has the same configuration as the auxiliary. This is a useful mnemonic and is illustrated for an (*S*)-oxime ether in Scheme 9.



Scheme 9

However, what is the origin of this diastereoselectivity? Although the exact conformation of the oxime ethers in solution is unknown, we assume that they are effectively planar due to appreciable conjugation of the oxygen lone pair; the almost planar structure of ROPHy/SOPHy oxime ethers is supported by X-ray studies, which also show that the sp^2-carbon and the substituent on oxygen are *trans* about the N–O bond in the solid state. The crystal structures of the SOPHy oximes of 2-naphthaldehyde, thiazole-2-carboxaldehyde, cinnamaldehyde and ferrocenecarboxaldehyde are shown in Fig. 2, and in all structures, the phenyl ring of the auxiliary adopts a conformation in which it is almost perpendicular to the planar CH=N–O oxime unit. Calculations at the semi-empirical level support the fact that (in the gas phase) the *trans*-orientation about the N–O bond is the more stable, and that there is a high barrier to rotation about the N–O bond — *ca.* 32 kJ mol^{-1} for the oxime ether MeCH=NOCH$_2$Ph. Interestingly, they also show that the conformation adopted by the phenyl ring (as shown in the X-ray crystal structures) is the minimum energy conformation in the gas phase, and hence, in view of the low solvating power of toluene, probably also in solution. In the cases of the oxime ethers shown in Fig. 2, the stereochemical result of their reaction involves addition of the nucleophile to the face opposite from the phenyl group, an outcome equivalent to that shown in Scheme 9.

However, rationalisations based on solid state structures, although useful in a predictive sense, may bear little relevance to a reaction carried out in solution in the presence of a Lewis acid. Although, the exact nature of the reacting oxime ether species in solution is not known, *ab initio* Hartree–Fock calculations with the

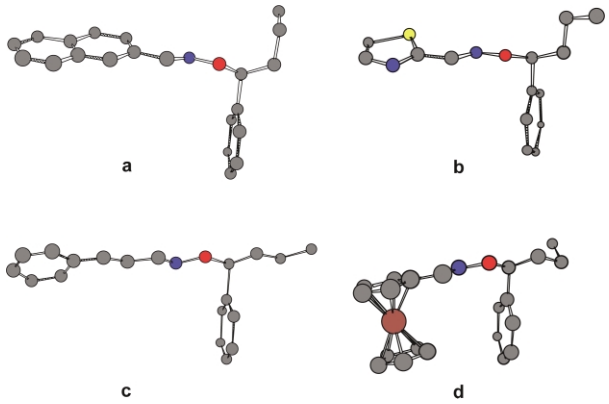
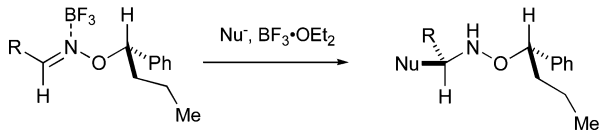


Fig. 2 X-Ray crystal structures of SOPHy oximes of (a) 2-naphthaldehyde, (b) thiazole-2-carboxaldehyde, (c) cinnamaldehyde and (d) ferrocene-carboxaldehyde.

6–31G(d,p) basis set suggest that there is a preference of *ca.* 10 kJ mol^{-1} for complexation of the boron trifluoride to nitrogen rather than oxygen of MeCH=NOCHPhPr. Hence we assume that the BF_3 will bind to the nitrogen atom, and that minimum steric interactions will dictate the conformation shown in Scheme 10, assuming the



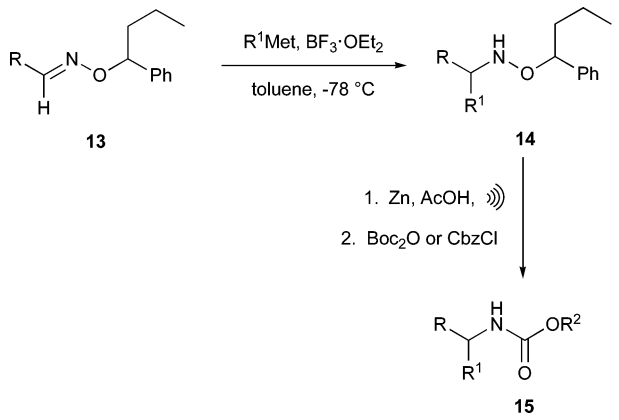
Scheme 10

trans arrangement about the N–O bond is maintained in solution. This conformation is analogous to that proposed in allylic systems to minimize $A_{1,3}$-strain. However, the calculations also suggest that complexation significantly lowers the barrier to rotation about the N–O bond. Hence the involvement of non-planar non-*trans*-conformations of the oxime ether as the reacting species cannot be ruled out. Unfortunately, none of these explanations adequately explain the poor result obtained with the α-naphthylethyl auxiliary or why the α-phenylbutyl group is more effective than α-phenylethyl, although it is noteworthy that a recent publication also reports enhanced diastereoselectivity in additions to *N*-α-phenylbutyl imines compared to their *N*-α-phenylethyl counterparts.[30]

Asymmetric synthesis of amines

A large range of aldoxime ethers can be readily prepared by reaction of the corresponding aldehyde with either ROPHy or SOPHy, or more conveniently from the *N*-phthaloyl derivative of ROPHy or SOPHy by hydrazine hydrate mediated deprotection followed by *in situ* reaction with the aldehyde. Alkyl, cycloalkyl, aromatic and heteroaromatic aldehydes all react satisfactorily. The (*E*)-aldoxime ethers are separated from the (*Z*)-isomers, the amount of which varied from 0 to *ca.* 35% according to the nature of the aldehyde substituent. We have also studied ketoxime ethers, although, in general, their reactions exhibit poorer diastereoselectivity. The aldoxime ethers **13** readily undergo addition of organolithium and Grignard reagents under the standard conditions to give a wide range of hydroxylamines **14** in good yield and diastereoselectivity, although Grignard reagents appear to only add efficiently to oximes of aliphatic aldehydes.[31] Our first application of this chemistry was in the asymmetric synthesis of amines. Hence the N–O bond in hydroxylamines was readily cleaved using the zinc/acetic acid/ultrasound protocol,[32] and the resulting amine was protected without purification as either its *tert*-butyl or benzyl carbamates, the latter carbamate being used to introduce a chromophore to aid HPLC analysis. The carbamates were often solids, and could be purified further by recrystallisation. The enantiomeric purity of the *N*-protected amines **15** was determined by HPLC analysis using a chiral stationary phase by comparison

with the racemic product. As expected the observed ee of the amine derivatives **15** closely followed the de of the hydroxylamines **14**. A wide range of amines has been synthesised by this method as summarised in Scheme 11 and Table 3.[31]



Scheme 11

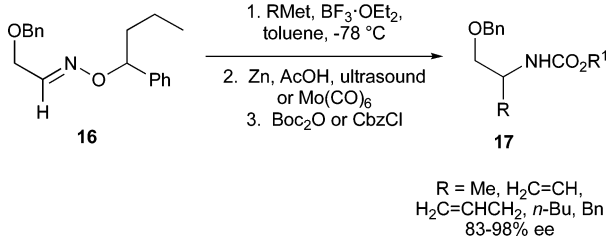
Table 3 Addition of organometallic reagents to *O*-(1-phenylbutyl) aldoximes

R	R^1	**14** Yield/ de (%)	R^2	**15** Yield/ ee (%)
n-Pr	*i*-Pr	70/ > 90	Bn	58/91
n-Pr	Bn	21/ > 90	Bn	85/97
i-Pr	Allyl	78/86	Bn	47/78
$CHEt_2$	Allyl	100/96	Bn	75/91
$BnO(CH_2)_4$	*n*-Pr	98/ > 95	*t*-Bu	85/88
$BnO(CH_2)_4$	Ph	61/83	*t*-Bu	31/77
c-Hex	*n*-Bu	95/ > 90	Bn	79/96
c-Hex	*t*-Bu	68/ > 90	Bn	25/96
c-Hex	Ph	77/ > 90	Bn	62/100
c-Hex	allyl	80/96	Bn	67/92
Bn	*i*-Pr	92/91	Bn	37/98
Bn	*n*-Bu	72/ > 96	*t*-Bu	78/ > 96
Bn	*i*-Bu	67/ > 96	*t*-Bu	67/ > 96
Ph	*n*-Bu	72/ > 95	Bn	87/92
Ph	Allyl	100/92	Bn	66/95
4-$MeOC_6H_4$	Allyl	80/96	Bn	62/98

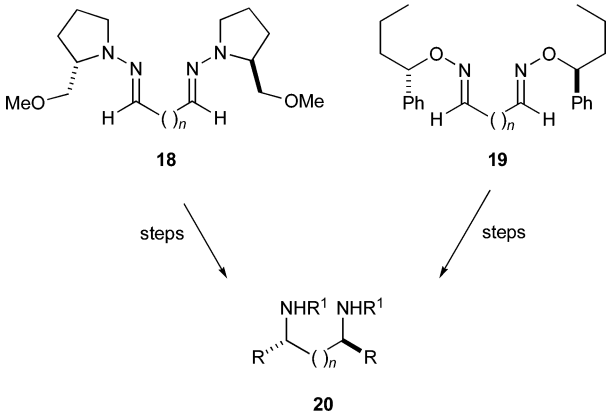
Since oxime ethers are known to be good radical acceptors, the addition of alkyl radicals to the SOPHy oxime of benzaldehyde, (*S*)-**13** (R = Ph) was briefly investigated. Using the conditions developed by Naito *et al.*,[7,8] we found that the addition of isopropyl and ethyl radicals (from the corresponding iodoalkanes) to the oxime ether did give the desired hydroxylamines **14**. However in both cases the yield was poor, and the diastereoselectivity was worse (85% and 51% de respectively) than that generally observed in the addition of organometallic reagents.

The method was extended by Alex Larigo to the asymmetric synthesis of 1,2-aminoalcohols using the ROPHy/SOPHy derived oxime ethers **16** of commercially available benzyloxyacetaldehyde as starting material. Addition of organolithium or Grignard reagents followed by N–O bond cleavage and *N*-protection gives a range of protected 1,2-aminoalcohols **17** in excellent ee (Scheme 12).[33]

Attempts to extend the methodology to the asymmetric synthesis of 1,*n*-diamines were less successful. By analogy with Enders' work on bis-SAMP-hydrazones **18**,[34] it was expected that bis-SOPHy-oxime ethers **19** would lead to chiral 1,*n*-diamines **20** (Scheme 13). In the event, the process foundered at the first step: both glyoxal and glutaraldehyde gave poor yields of the SOPHy oxime ethers, and their subsequent addition reactions were extremely disappointing — poor yields and stereocontrol.

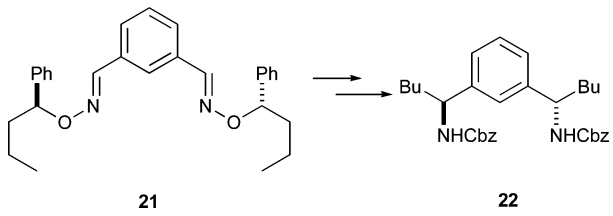


Scheme 12



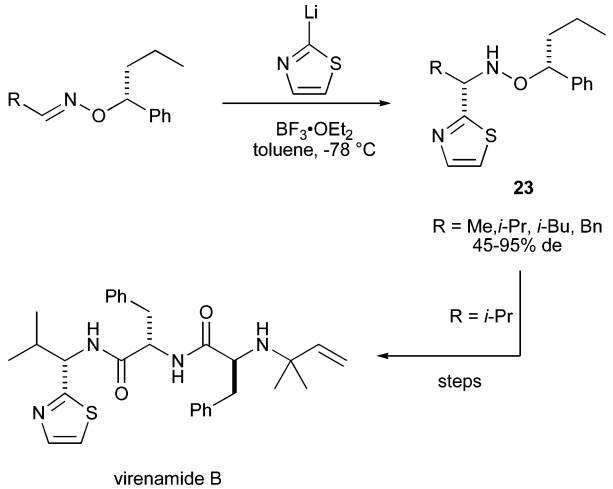
Scheme 13

The reaction was more successful with aromatic dialdehydes. Thus for example, the bis-SOPHy-oxime ether **21** of isophthaldialdehyde could be converted into the protected diamine **22** in reasonable yield (Scheme 14).[35]



Scheme 14

Finally, given the presence of the 1-(2-thiazolyl)ethylamine unit in a number of naturally occurring peptide derivatives, Jim Hunt investigated the asymmetric synthesis of such amines. A range of ROPHy-oxime ethers underwent addition of 2-lithiothiazole to give the hydroxylamines **23** in good yield and modest to excellent de (Scheme 15).[36] The isopropyl derivative **23** (R = *i*-Pr; > 95% de)



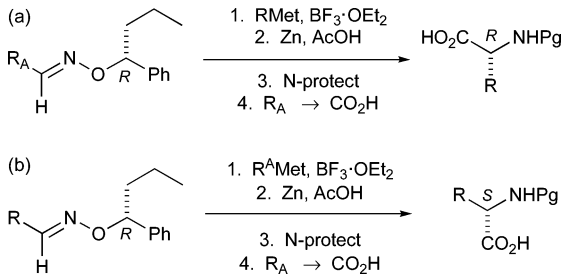
Scheme 15

was then converted into the cytotoxic thiazole-containing peptide virenamide B, isolated from the Australian ascidian *Diplospoma*

virens by N–O bond cleavage, followed by conventional peptide coupling reactions.[37]

Asymmetric synthesis of α- and β-amino acids

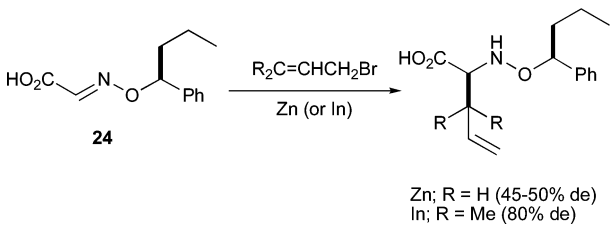
In order to adapt our asymmetric synthesis of protected amines into a route to *N*-protected α-amino acids, two strategies were considered (Scheme 16). The first involved the use of an oxime



Scheme 16

ether which incorporates the carboxylic acid precursor, R_A; addition of organometallic reagents, followed by cleavage of the N–O bond, *N*-protection and conversion of R_A into a carboxyl group would then give the required amino acid. Alternatively the carboxyl synthon can be added as an organometallic reagent, R_AMet (Scheme 16b), to the oxime ether, the two routes being stereo-complementary, since one enantiomer of the 1-phenylbutyl auxiliary can give both enantiomers of the α-amino acid.

As mentioned above, the first strategy had already been briefly investigated by Hanessian *et al.* in a study of the glyoxylamide derived from Oppolzer's camphorsultam that gave good to excellent diastereoselectivity (62–98% de) when reacted with allylzinc reagents,[16] Adapting this approach, we prepared the SOPHy-oxime ether **24** of glyoxylic acid, and studied its addition reactions (Scheme 17).[35,38] Allylzinc added in good yield, but the

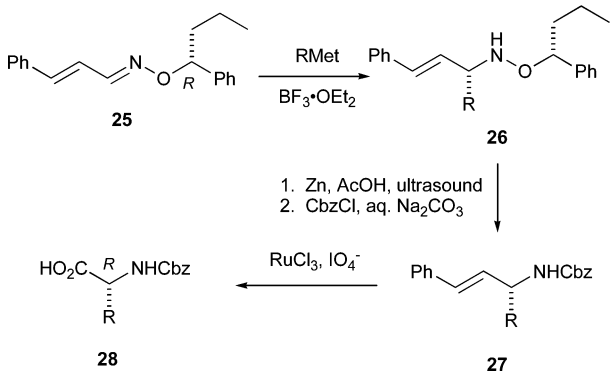


Scheme 17

diastereoselectivity was poor (45–50% de). Likewise the zinc reagent from dimethylallyl bromide added with poor diastereoselectivity, but after optimisation, we found that diastereomeric excesses of about 80% could be obtained with the corresponding indium reagent. Further improvements in de using a range of glyoxylic esters and amides were not observed, and therefore this approach was abandoned in favour of using a carboxyl precursor in the oxime ether.

The first carboxyl precursor investigated by Andy Lightfoot was the furan ring. However the ROPHy-oxime ether of 5-methylfurfural gave poor diastereoselectivity (59–83% de) in the addition of organometallic reagents and therefore an alternative oxime ether **25**, namely that derived from cinnamaldehyde, was investigated. This proved highly satisfactory and resulted in the asymmetric synthesis of a range of *N*-protected amino acids **28** (Scheme 18, Table 4), although the yields in the oxidative cleavage of the alkene were modest.[38–40]

The method could also be used for ketoxime ethers derived from benzylidene acetone, although the diastereoselectivities were poorer, and the resulting α-methyl-α-amino acids were only formed in *ca.* 80% ee.[40] An alternative route to α-methyl-α-amino acids started from the (*E*)-SOPHy-oxime ether of acetophenone, which underwent addition of *n*-butyllithium with 94% de. Subsequent N–O bond cleavage, *N*-acetylation and oxidative cleavage of the phenyl ring with Ru(VIII) gave *N*-acetyl-α-methylnorleucine, although the yields were poor.[38]



Scheme 18

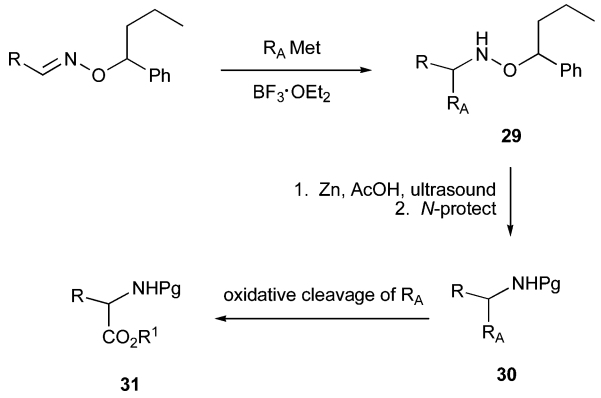
Table 4 Synthesis of (*R*)-*N*-Cbz-amino acids from the ROPHy oxime of cinnamaldehyde **25**

R	**26** Yield/ de (%)	**27** Yield (%)	**28** Yield (%)
Me	95/92	31	25
n-Bu	92/93	83	57
i-Bu	93/92	86	36
Ph	76/90	66	55
4-F-3-Me-C_6H_3	30/81	52[a]	23[a]

[a] Boc-protecting group in place of Cbz

The second strategy, involving addition of the carboxyl synthon as the organometallic reagent, R_AMet (Scheme 16b), was then investigated by Tracey Cooper and Pierre Laurent. The group R_A that was chosen for initial study was again the furan group, since 2-furyllithium is readily generated, and oxidation of the furan ring with a range of reagents gives the carboxylic acid. Thus 2-furyllithium was added to the oxime ether according to our normal protocol. However, the results were generally disappointing - poor yields (14–40%) and modest diastereoselectivity (52–95% de). The second organometallic carboxyl synthon investigated was phenyllithium, since the benzene ring can also be cleaved oxidatively to give a carboxylic acid. The additions proceeded with excellent diastereoselectivity (> 95% de) to give the hydroxylamines **29**, although the yields were poor (< 40%). Finally the use of vinyl organometallic reagents as carboxyl synthons was investigated. Vinylmagnesium bromide (as supplied commercially in THF) did not add to the oxime ethers. However vinyllithium added smoothly to a range of oxime ethers to give the corresponding hydroxylamines **29** in generally acceptable yield and diastereoselectivity, proving to be the best nucleophilic carboxyl synthon. With a range of chiral hydroxylamines **29** containing a carboxylic acid precursor, R_A, in hand, their conversion into α-amino acid derivatives was undertaken. This was achieved by initial cleavage of the N–O bond using the previously described zinc/acetic acid/ultrasound method. The resulting amines were immediately converted into their *tert*-butyl or benzyl carbamates or *N*-acetyl derivatives by reaction with di-*tert*-butyl dicarbonate, benzyl chloroformate or acetic anhydride respectively. The *N*-protected amines **30** were isolated in varying yield, and their enantiomeric purity established by HPLC on a chiral stationary phase. The conversion of the R_A substituent in the *N*-protected amines **30** into a carboxylic acid (or ester) **31** was carried out under standard oxidative conditions — Ru(VIII) or using Marshall's ozonolysis procedure which leads directly to the methyl ester.[41] A range of α-amino acid derivatives was thus prepared, including derivatives of 4-bromophenylalanine, *tert*-leucine, norvaline, cyclohexylglycine, phenylglycine, 4-methoxyphenylglycine, glutamic acid, 2-amino-

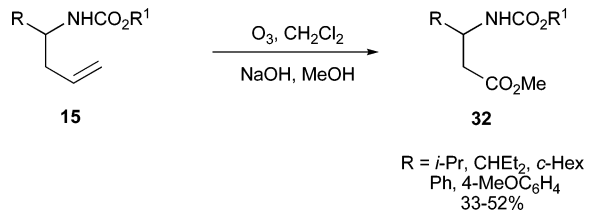
8-oxodecanoic acid (Aoda, a component of the cyclic peptide apicidin — also see below), these last two examples involving simultaneous oxidative cleavage of the alkene in the side chain. The results are summarised in Scheme 19 and Table 5.[42] In addition, one



Scheme 19

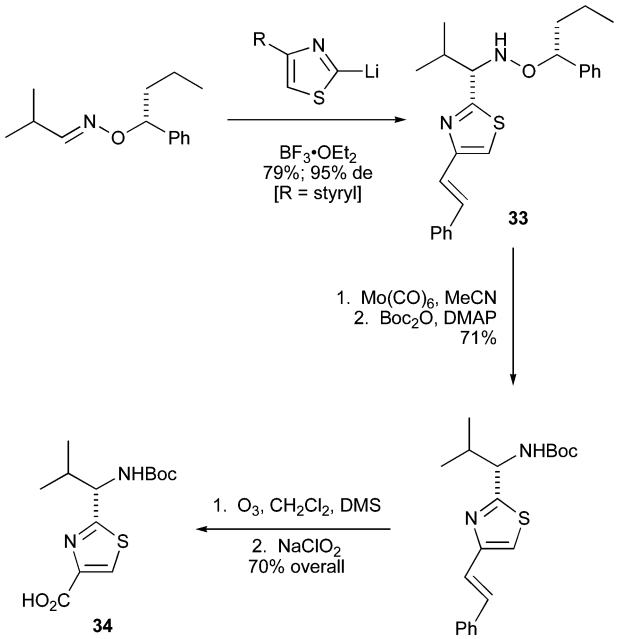
example of an α-methyl-α-amino acid was prepared by this route; (*S*)-*N*-Cbz-α-methylvaline was obtained by addition of vinyllithium to the ROPHy-ketoxime ether of 3-methylbutan-2-one (54% yield, > 95% de), followed by functional group transformation.

With a range of chiral homoallylamines **15** (R = allyl) in hand (Scheme 11, Table 3), their conversion into β-amino acid derivatives was relatively trivial, and involved ozonolysis to give the *N*-protected β-amino esters **32** (Scheme 20).[31]



Scheme 20

In an extension of this chemistry, and following preliminary work by Joanne Pinder, Alex Larigo was able to prepare chiral 2-(1-aminoalkyl)thiazole-4-carboxylic acids, building blocks for a number of thiazole-containing natural products. For example, the 2-lithiothiazole derived from 2-bromo-4-styrylthiazole, added with high diastereoselectivity (95% de) to the ROPHy-oxime ether of isobutyraldehyde to give the expected hydroxylamine **33**. Cleavage of the N–O bond using molybdenum hexacarbonyl, followed by *N*-protection, and a two-stage oxidative cleavage of the alkene gave the (*S*)-thiazole **34** in good yield (Scheme 21).[43]



Scheme 21

Asymmetric synthesis of 2-substituted nitrogen heterocycles

The asymmetric synthesis of nitrogen-containing heterocyclic compounds such as pyrrolidines and piperidines is an area of considerable interest due to presence of such rings in a number of biologically important compounds. Our first foray into this arena started in 1996 when Andy Lightfoot undertook the synthesis of simple piperidines such as the hemlock alkaloid (*R*)-(−)-coniine **36**, a molecule contained within the poisoned chalice used by Socrates to take his own life, wonderfully depicted in the picture by Jacques-Louis David, the original of which hangs in The Metropolitan Museum of Art, New York (see http://metmuseum.org/collections/view1.asp?dep = 11&item = 31.45).

Coniine, isolated from hemlock (*Conium maculatum*) (Fig. 3) is a simple 2-substituted piperidine, which, unusually, occurs naturally in both enantiomeric forms. Our synthesis of the (*R*)-enantiomer starts from the SOPHy oxime of butyraldehyde with addition of pentenylmagnesium bromide at *ca.* −90 °C to give the hydroxylamine **35** in both excellent yield (94%) and diastereomeric excess (> 95%). The N–O bond was cleaved using the usual zinc/acetic acid/ultrasound protocol, and the resulting amine protected as its benzyl carbamate. Oxidative cleavage of the double bond was followed, somewhat to our surprise, by immediate cyclisation and dehydration to give the ene-carbamate **36** in modest yield. Finally, treatment with hydrogen and palladium-on-carbon catalyst resulted in reduction of the alkene and hydrogenolysis of the Cbz-group to give (*R*)-(−)-coniine (Scheme 22).[44] In a variation, in which the oxidation of the alkene was carried out using $RuCl_3$–$NaIO_4$, the corresponding lactam could be isolated, which after hydrogenolysis gave the lactam **37** (Scheme 22).[45]

The method was extended to the synthesis of (+)-pseudoconhydrine as shown in Scheme 23. The enantiomeric ene-carbamate (*S*)-**36**, prepared from the ROPHy oxime of butyraldehyde in an

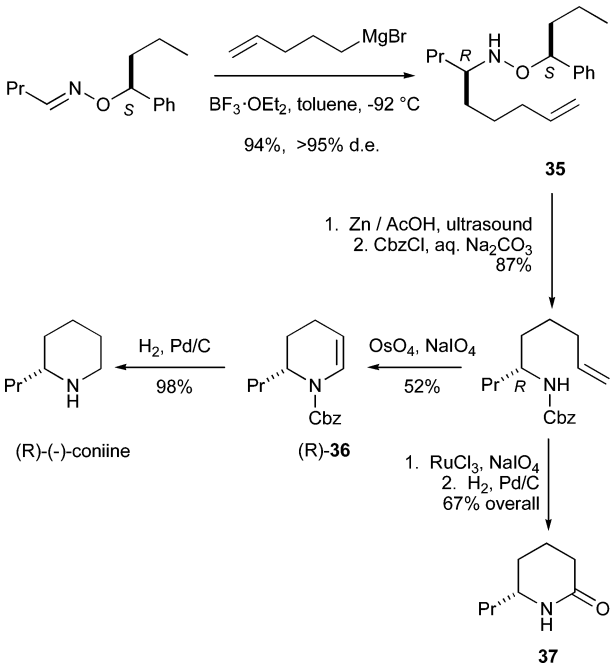
Table 5 Synthesis of *N*-protected amino acids from *O*-(1-phenylbutyl) aldoximes

R	R_A	**29** Yield/ de (%)	Pg	**30** Yield/ ee (%)	R^1	**31** Yield (%)
4-$BrC_6H_4CH_2$	2-furyl	40/83	Boc	72/83	H	33
t-Bu	Ph	32/ > 98	Ac	28/ > 98	H	63
n-Pr	Vinyl	87/84	Cbz	89/nd	Me	59/86%ee
H_2C=CH$(CH_2)_2$	Vinyl	77/94	Cbz	53/nd	Me	40/93%ee
c-Hex	Vinyl	74/92	Cbz	52/nd	Me	70
EtC(= CH_2)$(CH_2)_5$	Vinyl	76/ > 95	Cbz	70/97	H	39
Ph	Vinyl	46/98	Ac	9/90	H	24
4-$MeOC_6H_4$	Vinyl	50/91	Cbz	85/nd	Me	58

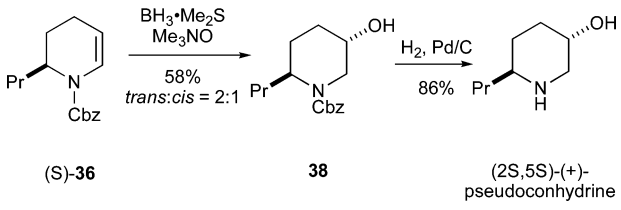
nd = not determined

(R)-coniine

Fig. 3 Hemlock (*Conium maculatum*) and (*R*)-coniine, one of the constituent alkaloids (picture William & Wilma Follette @ USDA-NRCS PLANTS Database / USDA NRCS. 1992. *Western wetland flora: Field office guide to plant species.* West Region, Sacramento, California, USA).



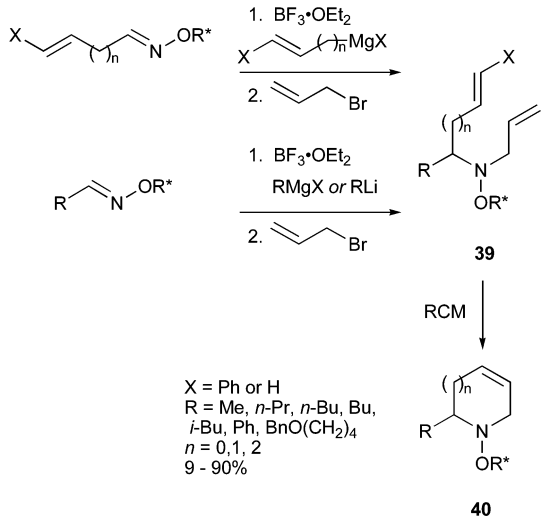
Scheme 22



Scheme 23

identical manner, was converted into the hydroxypiperidine **38** by hydroboration–oxidation to give the desired *trans*-diastereomer **38** as the major product (*ca.* 2 : 1). Finally hydrogenolysis of the Cbz-group gave (+)-pseudoconhydrine in excellent yield.[44]

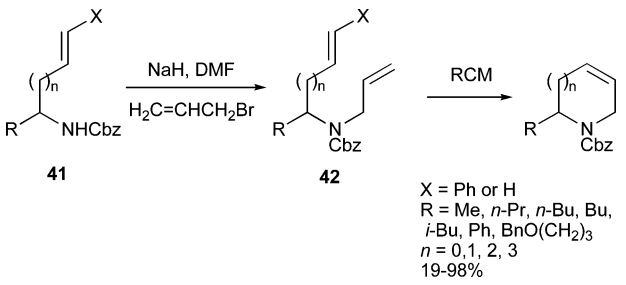
One of the major advances in synthetic chemistry during the 1990s was the development of practical and reliable catalysts for ring-closing metathesis (RCM) by Grubbs and others. Hence we decided to investigate the combination of the highly diastereoselective addition reactions of ROPHy/SOPHy oximes with the RCM reaction in the asymmetric synthesis of nitrogen heterocycles. The substrates for the RCM reaction are accessible either by the addition of an organometallic reagent to an oxime ether derived from an unsaturated aldehyde, or by the addition of an alkene containing organometallic reagent to an aryl or alkyl aldoxime ether, followed in both cases by *N*-allylation of the resulting hydroxylamine (Scheme 24). Jim Hunt and Pierre Laurent showed



Scheme 24

that both approaches were viable, and a range of oximes was converted into hydroxylamines with excellent diastereocontrol. Reaction with allyl bromide gave dienes **39** which upon treatment with benzylidene bis(tricyclohexylphosphino)dichlororuthenium (Grubbs' catalyst) gave the expected nitrogen heterocycles **40** (Scheme 24).[46,47]

Although the above results indicated that the presence of a basic and nucleophilic hydroxylamine nitrogen atom did not adversely affect the RCM reaction, an alternative set of substrates in which the N–O bond had been previously cleaved was also investigated. Thus the carbamates **41**, prepared by the usual methods, were converted into the corresponding *N*-allyl derivatives **42** (Scheme 25). The RCM reaction proceeded smoothly to give a range of 5-

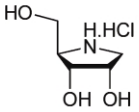


Scheme 25

and 6-membered nitrogen heterocycles in good yield. The yield of the 7-membered ring was somewhat lower, whilst the 8-membered ring was formed in poor yield.[46,47] The heterocycles arising from the oxime addition-RCM sequence readily underwent further transformations, resulting in a second synthesis of (*R*)-(−)-coniine.

The versatility of the oxime addition-RCM sequence was further illustrated by the synthesis of the iminosugar 1,4-dideoxy-1,4-imino-D-ribitol **47**, a natural product isolated from the white mulberry tree *Morus alba* (Fig. 4).

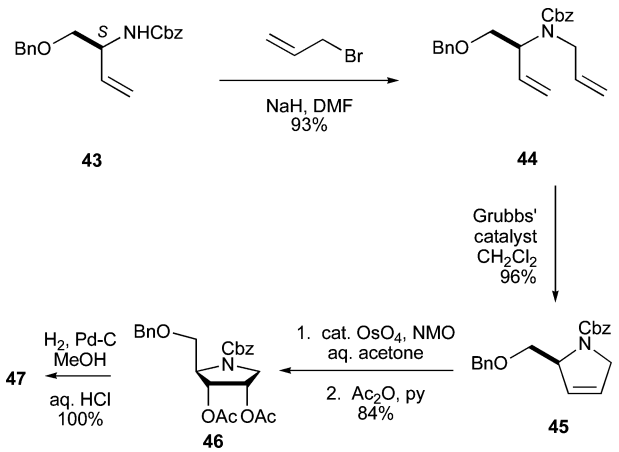
Addition of vinyllithium to the SOPHy oxime **16** of benzyloxyacetaldehyde followed by the usual N–O bond cleavage and *N*-



1,4-dideoxy-1,4-imino-D-ribitol
47

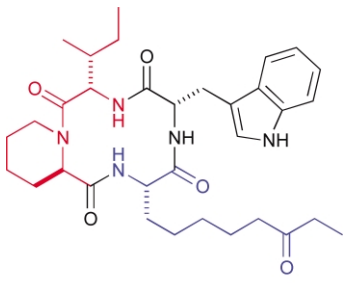
Fig. 4 White mulberry tree (*Morus alba*) and 1,4-dideoxy-1,4-imino-D-ribitol **47**, one of the constituent iminosugars (picture downloaded from http://botit.botany.wisc.edu:16080/images/401/Magnoliophyta/Magnoliopsida/Hamamelidae/Moraceae/Morus_alba/Lrg_bough_w_fruit_MC.html and used with permission of Michael W. Clayton).

protection gave the (*S*)-allylamine **43**. Alkylation with allyl bromide to give **44** was followed by a high yielding RCM reaction to give the dihydropyrrole **45**, dihydroxylation of which from the least hindered face with catalytic osmium tetroxide in the presence of *N*-methylmorpholine-*N*-oxide (NMO) gave, after acetylation, the protected iminosugar **46**. Hydrogenolysis of **46** in methanolic hydrochloric acid gave the natural product **47** in quantitative yield (Scheme 26).[33]



Scheme 26

The method was also applied in an approach to the isoleucine-pipecolic dipeptide sequence of apicidin A shown in red in Fig. 5.

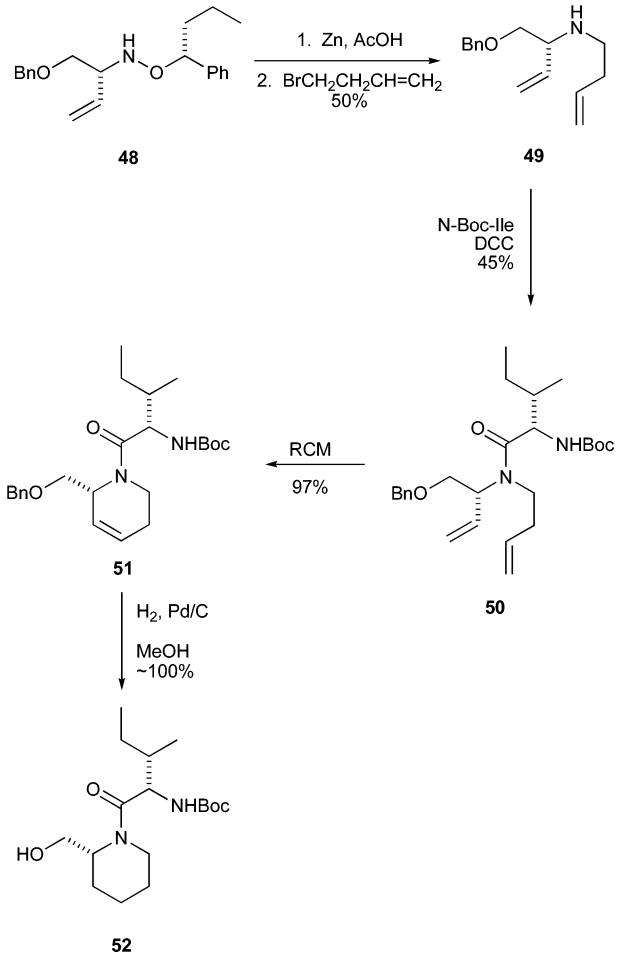


apicidin A

Fig. 5 Structure of apicidin A.

Apicidin A is a cyclic tetrapeptide comprising, in addition to this dipeptide fragment, tryptophan and 2-amino-8-oxodecanoic acid (Aoda). We have already described an oxime based asymmetric synthesis (see above) of Aoda (shown in blue in Fig. 5), and therefore it seemed entirely appropriate to use oxime-based methodology to address the synthesis of the isoleucine-pipecolic dipeptide.

Thus the hydroxylamine **48**, prepared by addition of vinyllithium (89% de) to the ROPHy-oxime ether **16** of benzyloxyacetaldehyde, was treated with zinc/acetic acid to cleave the N–O bond; this was followed by alkylation with 4-bromobutene to give the amine **49**. Coupling to (*S*)-*N*-Boc-isoleucine gave the diene **50**, which underwent RCM reaction on treatment with Grubbs' catalyst to give the tetrahydropyridine **51**. Finally hydrogenation/hydrogenolysis gave the amino acid derivative **52** ready for oxidation of the alcohol to the carboxylic acid and subsequent peptide coupling (Scheme 27).[35]

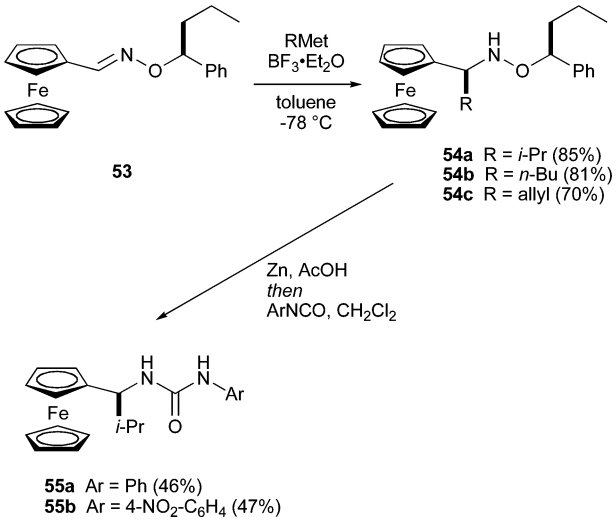


Scheme 27

Asymmetric synthesis of ferrocene derivatives; potential chiral redox-active receptors

The University of Exeter is "twinned" with the University of Rennes. During a visit to Rennes by a group of Exeter chemists in 2000, my inorganic chemistry colleague Jim Tucker, having had to sit through my seminar on asymmetric synthesis using oximes, asked me if the reaction would work on the oxime derived from ferrocenecarboxaldehyde, since the resulting α-ferrocenylalkylamines might be of interest in his work involving redox-active receptors. On our return to Exeter, I asked Pierre Laurent to investigate. Pierre soon found that he could easily prepare the crystalline SOPHy oxime **53** of ferrocenecarboxaldehyde, and that it underwent facile addition of organometallic reagents under our usual conditions to give the corresponding hydroxylamines **54** (70–85%) with truly excellent stereocontrol (>95% de). To investigate the binding of carboxylates to chiral ferrocene derivatives, a urea-based receptor was chosen. Thus the hydroxylamine **54a** was converted into the ureas **55** by cleavage of the N–O bond followed by reaction with the corresponding aryl isocyanate (Scheme 28).[48]

With the help of Jim Tucker and his research group, we were able to show that both the ferrocenyl ureas **55a** and **55b** bind carboxylate



53

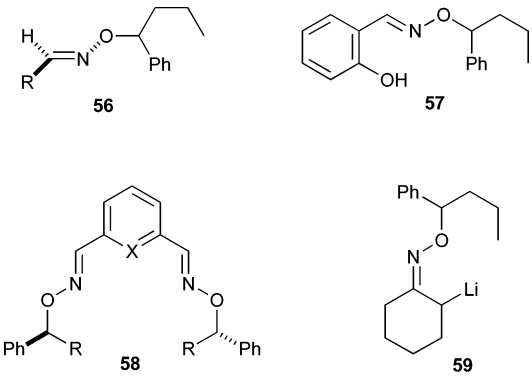
54a R = *i*-Pr (85%)
54b R = *n*-Bu (81%)
54c R = allyl (70%)

55a Ar = Ph (46%)
55b Ar = 4-NO_2-C_6H_4 (47%)

Scheme 28

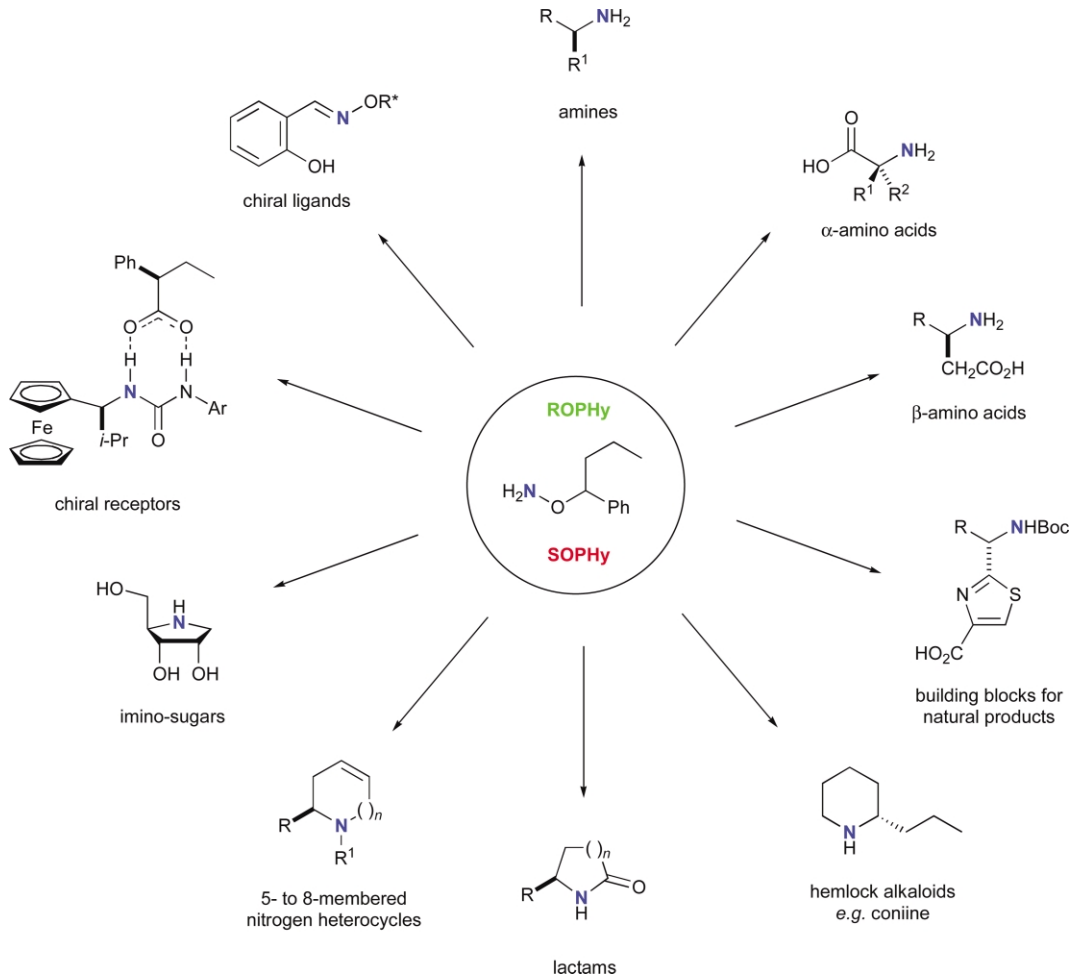
anions in CD_3CN solution as evidenced by the large downfield shifts (*ca.* +4 ppm) of the urea NH proton signals in the 1H NMR spectra of the host upon addition of aliquots of racemic tetra-*n*-butylammonium 2-phenylbutyrate. Job plots confirmed the stoichiometry as 1 : 1, and the titration data established the binding constant between **55a** and the racemic carboxylate in CD_3CN as 2080 M^{-1} (± 10%) at 293 K. The increased acidity of the urea NH protons in the 4-nitrophenyl urea **55b** resulted in stronger binding that was readily studied by UV-vis spectroscopy, and gave a binding constant between **55b** and the racemic carboxylate in DMSO as 2530 M^{-1} (± 10%). Studies with the enantiopure carboxylates gave binding constants of 2350 M^{-1} and 2910 M^{-1} for the (*S*)- and (*R*)-forms respectively, and show that there is the desired difference in binding between the chiral receptor and enantiomeric guests. The binding of carboxylates to the chiral ferrocene receptor **55b** was also detected by a cathodic shift of −70 mV in the redox couple of the ferrocene. However, no significant difference in the redox response of receptor **55b** to complexation of racemic and enantiopure forms of the carboxylate were observed.

Although Jim and I had been colleagues for 5 years, and were generally aware what each other were doing, it took a trip to France for the above collaborative project to develop. In fact without this adventitious visit to Rennes, it is doubtful whether we would ever have applied the ROPHy/SOPHy oxime methodology to metal-



56 **57** **58** **59**

Fig. 6 Future directions?



Scheme 29

locenes. In the event, chiral oxime ethers are very convenient precursors to chiral ferrocene, systems that are ideal starting points for the design of redox-active receptors with improved enantioselectivity.

Summary and future directions

As explained in the Introduction, our original intention had been to investigate cycloaddition reactions of the oxime C=N bond; more than ten years on we have still not started on this project! Nevertheless, face selective cycloaddition to the C=N bond in ROPHy/SOPHy-oxime ether dienophiles/dipolarophiles **56** (R = various) or 1-aza-1,3-dienes **56** (R = CX=CHR′) remains an intriguing question. Another early idea yet to reach fruition is the use of such oxime ethers as chiral ligands: a range of potential ligands was readily prepared, for example the salicaldehyde derivative **57** and the C_2-symmetric ligands **58** (X = CH or N; R = *n*-Pr or CH_2OH) (Fig. 6). However, even in the much investigated addition of diethylzinc to benzaldehyde, we only observed poor stereoselectivity (*ca.* 30% ee for ligand **57**). Finally, by analogy with the successful lithiation chemistry of Enders' RAMP/SAMP-hydrazones, we have speculated about oxime lithiation, *e.g.* **59**.

At the start of our work in this area (early 1990s), the only truly general chiral auxiliaries that could mediate asymmetric reactions of C=N bonds were Enders' RAMP/SAMP hydrazones.[9] Oxime ethers, despite their potential, had found relatively little use in asymmetric synthesis. Now, one decade later we believe that we have now demonstrated the potential of such compounds. The oxime ether method complements Enders' hydrazone based methodology and the more recently introduced *tert*-butanesulfinyl imines.[4–6] The main advantage of the oxime methodology lies in the fact that the initial products of the addition reactions are chiral hydroxylamines. Although we have not developed their chemistry, preferring to date to cleave the N–O bond to access the corresponding amines, these are potentially versatile compounds in their own right, for example in reverse Cope cyclisations.[49]

The diverse range of structures accessible using our ROPHy/SOPHy-oxime ether methodology is summarised in Scheme 29, and includes simple amines, α- and β-amino acids, heterocyclic building blocks of natural products, piperidine alkaloids, lactams, 5- to 8-membered ring nitrogen heterocycles, imino-sugars, chiral ferrocene based receptors, and chiral ligands. Fuelled by the importance of amines and their derivatives bearing a chiral centre at the α-position, the interest in asymmetric addition to C=N bonds continues unabated. We hope that ROPHy/SOPHy-oxime ethers have contributed to the methodology for such asymmetric processes.

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Notes and references

1 G. B. Jones and C. J. Moody, *Chem. Commun.*, 1988, 1009.
2 G. B. Jones, C. J. Moody, A. Padwa and J. M. Kassir, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1721.
3 R. Bloch, *Chem. Rev.*, 1998, **98**, 1407.
4 T. P. Tang and J. A. Ellman, *J. Org. Chem.*, 1999, **64**, 12.
5 G. Borg, M. Chino and J. A. Ellman, *Tetrahedron Lett.*, 2001, **42**, 1433.
6 T. P. Tang, S. K. Volkman and J. A. Ellman, *J. Org. Chem.*, 2001, **66**, 8772.
7 H. Miyabe, R. Shibata, M. Sangawa, C. Ushiro and T. Naito, *Tetrahedron*, 1998, **54**, 11431.
8 H. Miyabe, A. Nishimura, M. Ueda and T. Naito, *Chem. Commun.*, 2002, 1454.
9 D. Enders and U. Reinhold, *Tetrahedron: Asymmetry*, 1997, **8**, 1895.
10 M. Busch and R. Hobein, *Chem. Ber.*, 1907, **40**, 2096.
11 A. Marxer and M. Horvath, *Helv. Chim. Acta*, 1964, **47**.
12 J. Pornet and L. Miginiac, *Bull. Soc. Chim. France*, 1975, 841.
13 A. Basha and D. W. Brooks, *J. Chem. Soc., Chem. Commun.*, 1987, 305.
14 T. Kolasa, S. K. Sharma and M. J. Miller, *Tetrahedron*, 1988, **44**, 5431.
15 Y. Yamamoto and W. Ito, *Tetrahedron*, 1988, **44**, 5415.
16 S. Hanessian and R.-Y. Yang, *Tetrahedron Lett.*, 1996, **37**, 5273.
17 Y. Ukaji, K. Kume, T. Watai and T. Fujisawa, *Chem. Lett.*, 1991, 173.
18 J. A. Marco, M. Carda, J. Murga, F. Gonzalez and E. Falomir, *Tetrahedron Lett.*, 1997, **38**, 1841.
19 K. Ikeda, K. Achiwa and M. Sekiya, *Tetrahedron Lett.*, 1983, **24**, 4707.
20 D. K. Pirie, W. M. Welch, P. D. Weeks and R. A. Volkmann, *Tetrahedron Lett.*, 1986, **27**, 1549.
21 K. E. Rodriques, A. Basha, J. B. Summers and D. W. Brooks, *Tetrahedron Lett.*, 1988, **29**, 3455.
22 H. Uno, T. Terakawa and H. Suzuki, *Synlett*, 1991, 559.
23 R. K. Dieter and R. Datar, *Can. J. Chem.*, 1993, **71**, 814.
24 For closely related more recent studies, see: N. Yamazaki, M. Atobe and C. Kibayashi, *Tetrahedron Lett.*, 2001, **42**, 5029.
25 W. Theilhacker and K. Ebke, *Angew. Chem.*, 1956, **68**, 303.
26 I. C. Choong and J. A. Ellman, *J. Org. Chem.*, 1999, **64**, 6528.
27 P. T. Gallagher, A. P. Lightfoot, C. J. Moody and A. M. Z. Slawin, *Synlett*, 1995, 445.
28 D. S. Brown, P. T. Gallagher, A. P. Lightfoot, C. J. Moody, A. M. Z. Slawin and E. Swann, *Tetrahedron*, 1995, **51**, 11473.
29 P. T. Gallagher, J. C. A. Hunt, A. P. Lightfoot and C. J. Moody, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2633.
30 Nancy, S. Ghosh, N. Singh, G. K. Nanda, P. Venugopalan, P. V. Bharatam and S. Trehan, *Chem. Commun.*, 2003, 1420.
31 J. C. A. Hunt, C. Lloyd, C. J. Moody, A. M. Z. Slawin and A. K. Takle, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3443.
32 D. Enders and H. Kempen, *Synlett*, 1994, 969.
33 T. S. Cooper, A. S. Larigo, P. Laurent, C. J. Moody and A. K. Takle, *Synlett*, 2002, 1730.
34 D. Enders and M. Meiers, *Angew. Chem. Int.*, 1996, **35**, 2261.
35 P. Laurent, PhD thesis, University of Exeter, 2002.
36 C. J. Moody and J. C. A. Hunt, *Synlett*, 1999, 984.
37 C. J. Moody and J. C. A. Hunt, *J. Org. Chem.*, 1999, **64**, 8715.
38 T. S. Cooper, PhD thesis, University of Exeter, 2001.
39 I. Chao, H. F. Lu and T. S. Chou, *J. Org. Chem.*, 1997, **62**, 7882.
40 C. J. Moody, P. T. Gallagher, A. P. Lightfoot and A. M. Z. Slawin, *J. Org. Chem.*, 1999, **64**, 4419.
41 J. A. Marshall and A. W. Garofalo, *J. Org. Chem.*, 1993, **58**, 3675.
42 T. S. Cooper, P. Laurent, C. J. Moody and A. K. Takle, *Org. Biomol. Chem.*, 2004, 265.
43 A. S. Larigo, unpublished work.
44 C. J. Moody, A. P. Lightfoot and P. T. Gallagher, *J. Org. Chem.*, 1997, **62**, 746.
45 J. C. A. Hunt, PhD thesis, University of Exeter, 1999.
46 J. C. A. Hunt, P. Laurent and C. J. Moody, *Chem. Commun.*, 2000, 1771.
47 J. C. A. Hunt, P. Laurent and C. J. Moody, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2378.
48 P. Laurent, H. Miyaji, S. R. Collinson, I. Prokes, C. J. Moody, J. H. R. Tucker and A. M. Z. Slawin, *Org. Lett.*, 2002, **4**, 4037.
49 N. J. Cooper and D. W. Knight, *Tetrahedron*, 2004, **60**, 243.