MELDOLA LECTURE. Recent Developments in Asymmetric Synthesis

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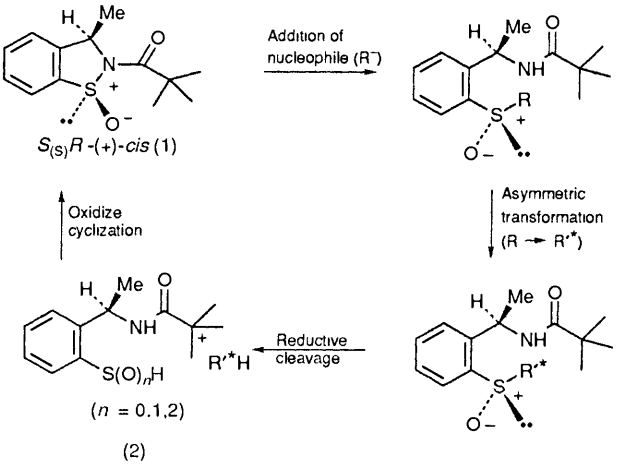
1 The Importance of Asymmetric Synthesis

The importance of enantiomerically pure molecules is now well accepted. These may be prepared by three broad methods, *viz.*, by asymmetric synthesis (which may be subdivided into stoicheiometric or catalytic methods), by starting from enantiomerically pure reagents (the 'chiral pool'), or by resolution. Each of these complementary approaches is of great importance in contemporary organic chemistry and each benefits from its own strengths and weaknesses. In our research group we have employed all of these methods for the synthesis of chiral molecules, although some form a greater part of our research than others. Our results will be discussed in the following sections.

2 Asymmetric Synthesis using Stoicheiometric Methods

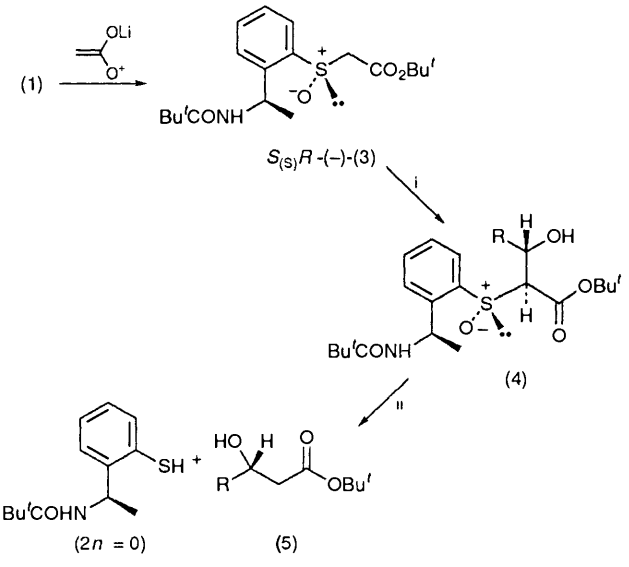
In 1989 we began a programme of research into a new class of chiral sulfoxide for asymmetric synthesis. Chiral sulfoxides are known to be excellent reagents for the stereocontrol of carbonyl reductions, aldol reactions *etc.*, however their synthesis and use has always resulted in destruction of the hard-won sulfur chirality.[1] Our intention from the start was to design a recyclable reagent which could be recovered and reused after the asymmetric transformation had been completed. However our reagent would still have to compete with others in terms of availability, stability, ease of use, and cost.

Our design concept is summarized in Scheme 1 and centres on the use of the chiral sulfinamide (1), which may be prepared in diastereoisomerically pure form in three steps from α-methylbenzylamine.[2-4] Reagent (1) is a configurationally stable material which we anticipated, on the basis of the known chemistry of such compounds, would react with carbon nucleophiles with predominant inversion of configuration at the sulfur atom to generate enantiomerically pure sulfoxides.[5] This could then be used to control the formation of a remote chiral centre, removed reductively to give the required enantiomerically enriched product together with the residue (2), which could subsequently be converted back into (1) *via* oxidation to the sulfinic acid.



Scheme 1

We first applied (1) to the control of the aldol reaction.[2,4] As anticipated the anion of *t*-butylacetate was effective at ring opening which proceeded with inversion of configuration as confirmed by an *X*-ray crystal structure analysis of the product (3).[4] Reaction of the anion derived from (3) with aldehydes generally gave adducts (4) with good to high selectivity, provided that the magnesium bromide enolate was used (Scheme 2, Table 1). In the case of Group I cations retro-aldolization was observed, which was a precedented process in related systems. Cleavage of the sulfoxide group in a representative number of examples was achieved using an aluminium amalgam which gave β-hydroxy esters (5) and the thiol (2) ($n = 0$) (Table 2). The latter could oxidized back to the sulfinic



Scheme 2 *Reagents and conditions*: i, 5 equiv. Bu^{t}MgBr, 3.0 equiv. RCHO, THF, −78 °C, 6h, then r.t. 6h; ii, Al/Hg amalgam, THF/H_2O, r.t.

Martin Wills was born in Swansea in 1964. He completed a B.Sc. degree at Imperial College in 1985 and a D.Phil. degree in 1988 at Oxford under the supervision of Dr. S. G. Davies. Following a one year postdoctoral fellowship with Professor W. Oppolzer at Geneva he was appointed to a lectureship at the University of Bath in October 1989. In 1994 he was awarded the Meldola Medal and Prize of the Royal Society of Chemistry. Dr. Wills is married to Jenny, and has a two year old son, Jonathan.

Table 1 Aldol reactions of $S_{(S)}R$-(−)-(3)

Product (4)	R	Yield(%)[a]	d c (%)
(a)	Ph	75	> 92
(b)	*p*-$MeOC_6H_4$	70	> 92
(c)	*m*-$MeOC_6H_4$	80	> 92
(d)	*o*-$MeOC_6H_4$	90	33
(e)	*p*-$NO_2C_6H_4$	70	> 92
(f)	*o*-$NO_2C_6H_4$	80	> 92
(g)	Bu^t	90	> 92
(h)	Pr^i	75	75
(i)	Me	60	50

[a] Yield of recrystallized compounds in case of (a) (b) (c) (e) (f) (g) [b] d e > 92% = single diastereoisomer in 270 MHz ^{1}H NMR spectrum of *crude* product

Table 2 Reductive cleavage reactions of the aldol adducts (4)

(4)	Yield of (5)(%)	e e % of (5)	Yield of (2)(%)
(a) (recrystallized)	85	> 92(*R*)	80
(f) (recrystallized)	65[a]	> 92(*R*)	—
(d) (2 1 mixture)	68	33(*R*)	—
(h) (7 1 mixture)	75	75(*R*)	73

[a] Nitro group was reduced to an amine

acid precursor of (1), as shown in Scheme 1, thus completing the recycling process [3,4] The configuration of the hydroxy esters (5) could be confirmed by comparing their optical rotations with those of known compounds, thereby confirming the relative configurations in the aldol adduct The aldol reaction stereochemistry may be explained if the reaction goes through the transition state shown in Figure 1 [3,4]

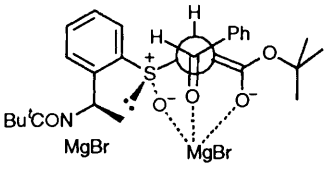
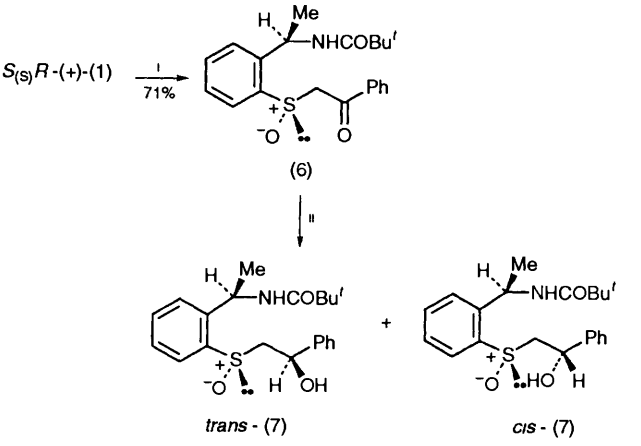


Figure 1 Transition state for aldol reactions

We have also employed (1) for the synthesis of allylic alcohols [6] In this case ketone enolates must be employed for the synthesis initially of β-keto sulfoxides (6) (a reaction which will not work with many of the other sources of sulfoxides such as sulfinate esters) The reduction of the carbonyl group to a β-hydroxy sulfoxide may be controlled by the choice of reducing agent so that either *trans*-(7) or *cis*-(7) is formed (Scheme 3, Table 3) Although in principle it is possible to remove the sulfur group reductively to give enantiomerically pure alcohols, we chose to apply the reduction to the synthesis of allylic alcohols through the use of the thermally initiated [2,3]sigmatropic sulfoxide elimination Two examples of our applications are shown in Scheme 4 and start from the appropriate keto-sulfoxide formed by the reaction of a cyclic ketone with (1) [6] This methodology has been applied to the synthesis of the muscone precursor (8) (Scheme 4) [6,7] In this sequence the side-products from the elimination (a sulfenic acid and the disulfide monoxide to which it condenses) may be reduced to thiol (2, $n = 0$) and thus sulfinamide (1) regenerated

In the application of (1) to the asymmetric synthesis of amines we chose a different approach [8,9] In this case the reaction of the anions of basic structure (9) with (1) results once more in ring-opening with inversion to (10) (Scheme 5) Reduction of the



Scheme 3 *Reagents and conditions* i, PhCOMe, $NaN(TMS)_2$, toluene, − 78 °C, ii, see Table 3

Table 3 Diastereoselective reductions of β-keto sulphoxide (6)

Reducing agent	Yield	*trans*-(7) *cis*-(7)
DIBAL-H	73%	94 6
NBu_4BH_4	quant	62 38
$NaBH_4$	quant	60 40
$NaBH_4/CeCl_3$	quant	57 43
$NaB(OAc)_3H$	quant	40 60
$LiAlH_4$	87%	25 75
DIBAL-H/$ZnBr_2$	80%	< 2 > 98

resulting adduct with DIBAL proceeded in high selectivity to furnish (11) Whilst this result has some precedent in the literature, we were surprised to observe that addition of an equivalent of zinc(II) bromide to the DIBAL resulted in complete reversal of the reduction selectivity and that the major product was (12) (Scheme 5, Table 4) The amide side chain in (10) is essential for this process, related substrates which lack this group give products with a much lower selectivity in the same reduction Chiral amines may be released from the reduction products by hydrolysis with mild acid, a reaction which regenerates the sulfinic acid (2, $n = 2$) ready for recyclization back to (1)

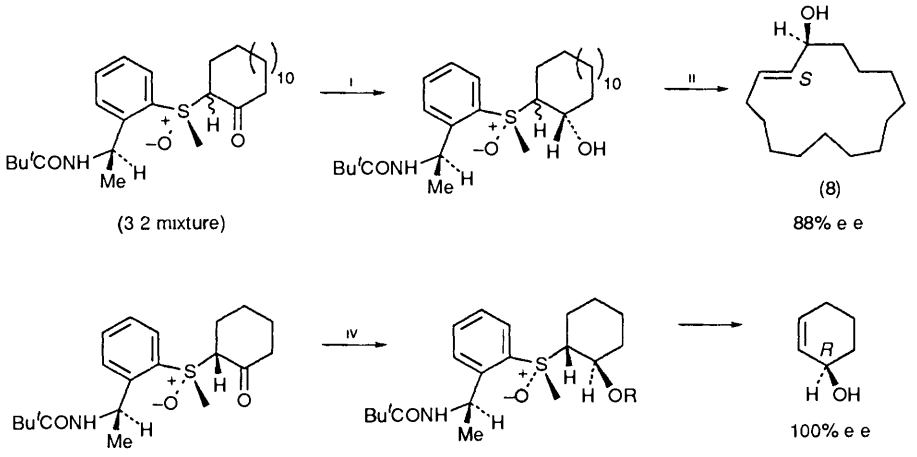
It is clear that (1) is a reagent with great promise, worthy of consideration in all applications in which sulfoxides are traditionally employed, it also benefits from the advantage of recyclability after the reactions to which it is applied

3 Asymmetric Synthesis using Catalytic Methods

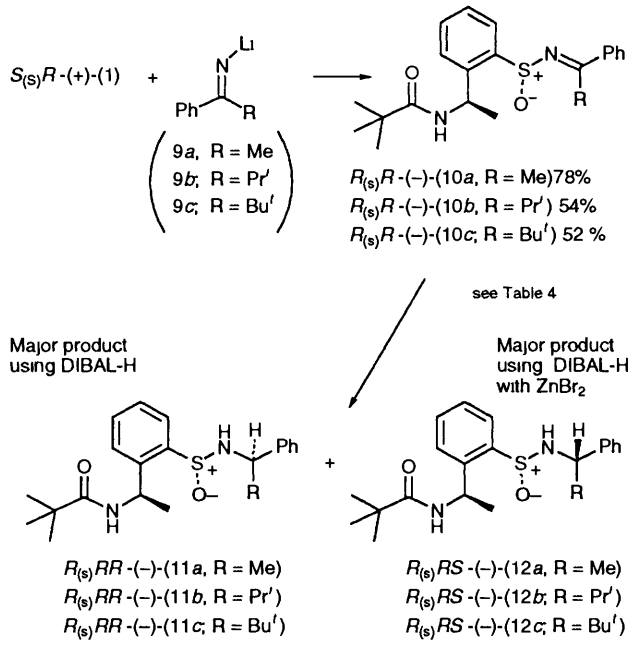
We are presently involved with the development of catalysts for a variety of asymmetric reactions Our choice of reactions has been chiefly guided by our interpretation of their versatility and importance in synthesis

3.1 Asymmetric Carbonyl Reduction

Many methods have been developed for the asymmetric reduction of ketones [10] This is a pivotal reaction in organic synthesis which provides an entry to the asymmetric synthesis of a very large number of target molecules One of the most impressive catalytic methods involves the use of a chiral oxazaborolidine (13) to activate the reaction between borane and a ketone whilst placing the reagents within a reactive distance of each other (Figure 2) [11] The resulting hydride transfer takes place predominantly to one face of the ketone and the product is released



Scheme 4 *Reagents and conditions* i DIBAL-H/$ZnBr_2$ THF, − 78°C, ii, toluene, 60°C, 5h, iii, (*R*)-$HO_2CC(OMe)(CF_3)Ph$, DCC, DMAP, iv, DIBAL-H, THF, − 78°C



Scheme 5

Table 4

Compound	Reagents	Yield	d e	Major isomer
(10a)	DIBAL-H THF − 23°C	98%	86%	(11a)
(10a)	$ZnBr_2$/DIBAL-H THF r t	94%	92%	(12a)
(10b)	DIBAL-H THF − 23°C	85%	71%	(11b)
(10b)	$ZnBr_2$/DIBAL-H THF r t	62%	86%	(12b)
(10c)	DIBAL-H THF − 23°C	82%	85%	(11c)
(10c)	$ZnBr_2$/DIBAL-H THF r t	56%	62%	(12c)

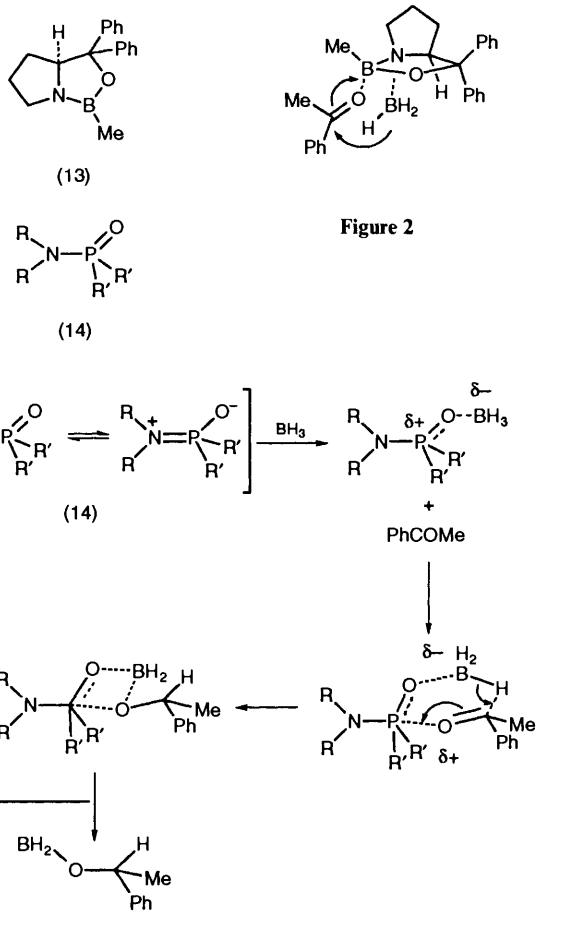
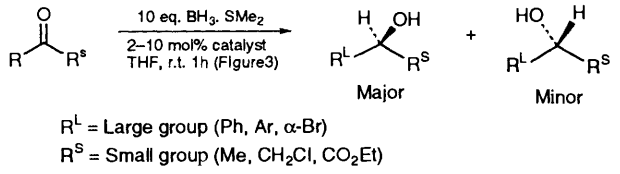


Figure 2

Scheme 6 Catalytic cycle for borane reduction of acetophenone mediated by (14)

immediately after, allowing the catalyst to complete further turnovers However, oxazaborolidines are highly sensitive to the presence of water in the reaction mixture and this can result in a dramatic decrease of the measured enantiomeric excesses

On the basis of what was known about the mode of action of oxazaborolidines, we proposed that phosphinamides (14), which are easy to prepare by a variety of methods and are stable to reductive conditions, would prove to be excellent catalysts for the reduction of ketones by borane [12 13] The mechanism by which they would operate in this respect is shown in Scheme 6 and depends critically on the initial donor interaction of the phosphinamide to the borane molecule The charge polarization in the resulting complex should make the phosphorus atom (which would not normally be considered to be a Lewis acid) an acceptor for a lone pair from the ketone This achieves activation of both reaction components and fixes their relative positions After hydride transfer, elimination of a borane alkoxide regenerates the catalyst for another turnover Our prediction proved to be correct (Scheme 7, Figure 3), treatment of acetophenone with one equivalent of borane in the presence of 10 mol% of the catalyst (15) (prepared by the reaction of α-methylbenzylamine with diphenylphosphinyl chloride[14])



Scheme 7

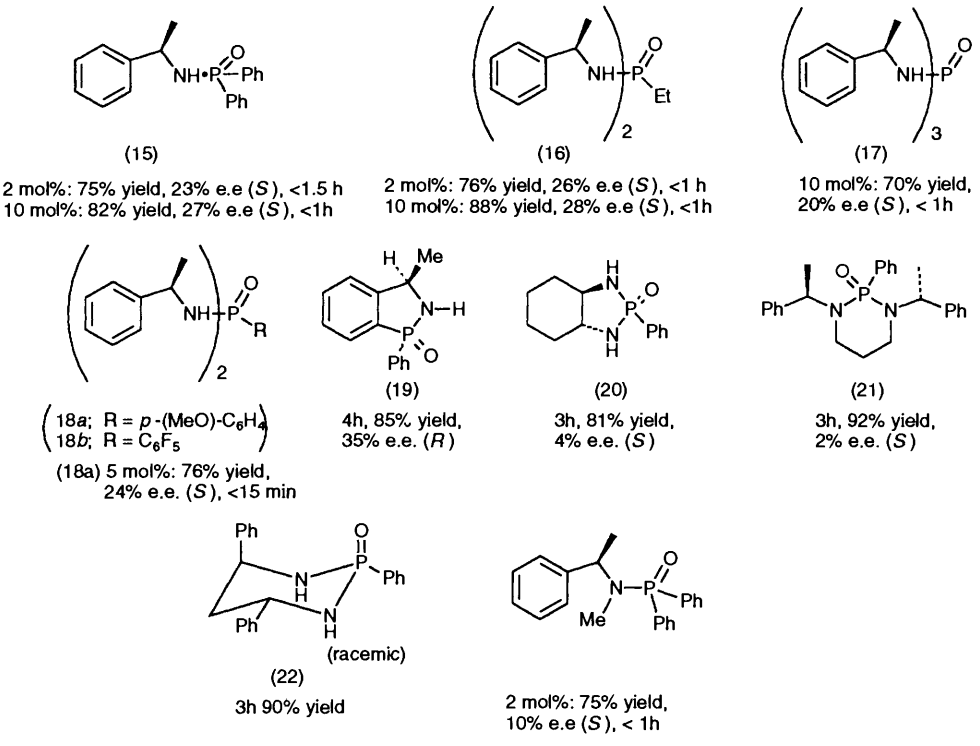


Figure 3 Asymmetric reductions of acetophenone mediated by N–P=O catalysts. Yield and e.e. of 1-phenethanol given for mol% catalyst employed (Scheme 7, R^L = Ph, R^S = Me).

resulted in complete reduction (> 99.95% by HPLC) within one hour. In contrast, the uncatalysed reaction was only 40% complete after this time. In fact a high level of acceleration was also observed using only 2 mol% of (15). The enantiomeric excess of the product, however, was low (25—30%).

We have continued this work through the synthesis and application of a number of derivatives of our initial catalyst, the results of which are summarized in Figure 3. We have found that catalysts containing two or three 'N–P=O' groups [*i.e.* (16) and (17)] may be employed, but this full functional unit is vital – triphenylphosphine oxide alone does not accelerate the reduction. The introduction of electron-donating groups such as *p*-methoxyphenyl in place of phenyl increases the activity [full reduction of acetophenone within fifteen minutes observed using 5 mol% (18a)] whilst electron withdrawing groups such as pentafluorophenyl, as in (18b), reduce the activity dramatically.[12,13] This supports our proposal of the mechanism of catalysis, in which the initial donation to borane is critical.

We have found that catalyst (15) is applicable to the asymmetric catalysis of the reduction of a wide range of ketones (Scheme 7, Figure 4). In all cases the absolute sense of the reduction was determined by the *size* difference between substituents, in the same way as oxazaborolidine catalysts. In most cases the enantiomeric excess was similar to the level achieved with acetophenone.

A remarkable stereoelectronic effect is also operative in our catalysts. Effective electron-donation from the nitrogen atom (which is sp^2 hybridized) to the P=O bond requires coplanarity

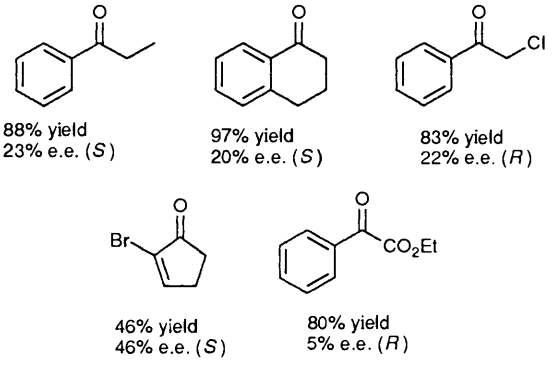


Figure 4 Reduction of ketones by borane/catalysts (15). Yields and e.e. given for reaction shown in Scheme 7

of the full 'R_2NPO' unit of the molecule (Figure 5). In this conformation donation from the nitrogen atom to the phosphorus *d*-orbital is presumably permitted. Certain cyclic phosphinamides, *e.g.* (19)—(22), are not able to achieve this conformation and are often very poor catalysts (Figure 6). There is a considerable amount of *X*-ray crystallographic evidence to show that the level of electron donation from the nitrogen atom in this situation is so low that it retains the sp^3 geometry characteristic of an amine.[15]

Having established the requirements of an effective reduction

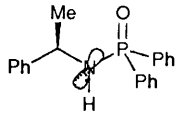


Figure 5 Orbital overlap in a good catalyst

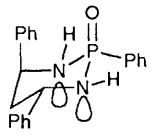
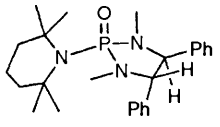


Figure 6 Orbital overlap not possible in a poor catalyst

catalyst we are now investigating methods for the improvement of the asymmetric inductions In particular we are combining a good donor amine with a conformationally rigid diamine unit as in (23) This will permit the synthesis of an active catalyst of known conformation which will allow us to predict the configuration of the major product enantiomer Another approach being taken is to address the electronic nature of the phosphorus atom Our results, together with preliminary molecular modelling studies,[16] suggest that the electron-donor properties of phosphinamides play a far greater role in their reactivity than their acceptor strength We are therefore investigating the combination of an acceptor site into a phosphinamide catalyst so that both reaction components in the reduction are held in a predictable position



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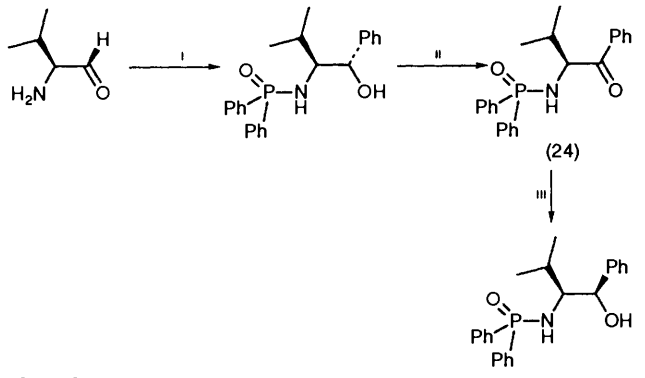
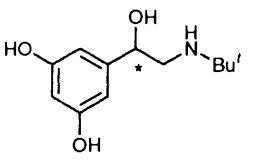
A further application of phosphinamides is as directing groups in an intramolecular sense An interesting preliminary result which hints at the value of the group is shown in Scheme 8 Reduction with borane of the valinol-derived ketone (24) resulted in formation of a single diastereoisomer (by ^{1}H-NMR) of a product which is epimeric to that of the starting amino alcohol [17] Whilst this stereoselectivity is not directed in an *asymmetric* sense by the phosphinamide, a far higher selectivity is achieved in the reduction than with most other nitrogen protecting groups (a 4 4 1 mixture is formed in the case of the *N*-*t*-butoxycarbamate group) β-Amino alcohols such as (25) to (27) are important molecules to the pharmaceutical industry, having found application as broncho- and vasodilators and peptide mimics [18]

3.2 A New Class of Ligand for Asymmetric Catalysis

Many important chemical reactions may be catalysed asymmetrically using a metal complex containing an appropriate enan-



Scheme 8 *Reagents and conditions* i, 5 eq PhMgBr, THF, − 78°C, 75%, ii, 5 mol% TPAP, 1 5 eq NMO, $CHCl_2$, 93%, iii, 2 5 eq BH_3 SMe_2, THF, 90%



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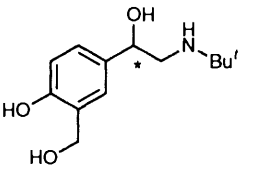

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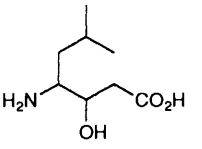

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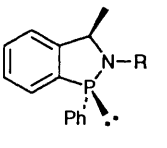

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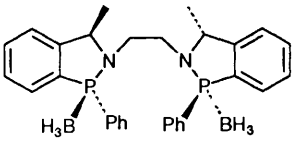

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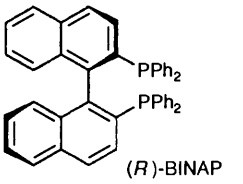
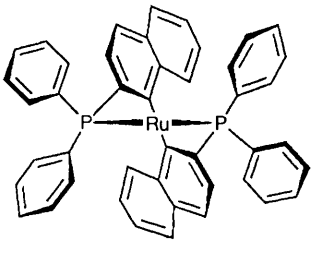


(30)

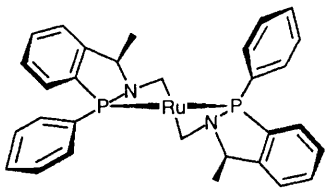
tiomerically pure ligand Whilst phosphine donors are the most widely used, nitrogen, sulfur, oxygen and other donor elements, or combinations thereof, have been employed in ligands A long-term aim of our group is to develop a general class of chiral ligand which may be 'fine-tuned' electronically or sterically, for particular applications Our strategy pivots upon the use of the enantiomerically pure benzazaphosphole unit (28), which contains a phosphorus donor atom and may be prepared from readily available α-methylbenzylamine (see below) Potentially monomer (28) may be used alone, or as a dimer through the coupling of two units, or in the form of a derivative in which it is attached to a second donor group (which may be based on phosphorus, oxygen, nitrogen *etc*) It is known that systems containing phosphorus–nitrogen single bonds are stable to hydrogenation and most conditions for asymmetric catalysis

Our rationale for the design of the ligands described above is the known importance of chiral environments created by appropriately oriented phenyl rings in asymmetric reactions We proposed, for example, that coordination of dimeric ligand (29) to a metal would result in the placement of four phenyl rings in the same three-dimensional arrangement as is the case for BINAP (30), one of the most successful ligands for asymmetric hydrogenation (Figure 7) Two of the phenyl rings are fused to the five-membered heterocyclic rings and their conformation is therefore fixed The remaining rings will adopt the essentially-orthogonal conformations shown to minimize steric interactions (Figure 8) Since benzazaphospholes are known to be somewhat air- and water-sensitive, they are prepared in the form of borane complexes The complexes between ruthenium (or other metals) and ligand (29) (or other ligands) will be prepared by *in situ* removal of borane by an amine, followed by addition



BINAP/Ru complex
[Ru(BINAP)(AcO)$_2$]

Figure 7

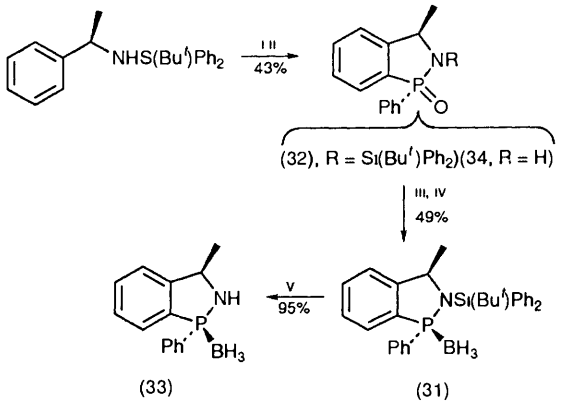


Deborated (29)–Ru complex

Figure 8

of a source of ruthenium following reported protocols The first steps in our development of a general class of catalyst are described below [19 20]

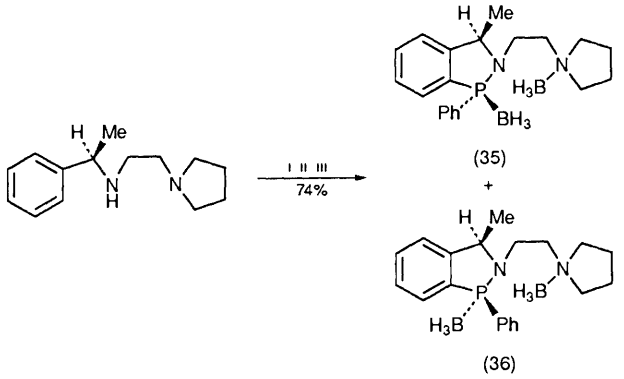
We prepared the borane-protected catalyst monomer (31) in two steps from protected α-methylbenzylamine *via* the route shown in Scheme 9 The *trans*-stereochemistry between methyl and phenyl groups for both (31) and the intermediate benzazaphosphole oxide (32), was confirmed by an *X*-ray crystal structure analysis [19 20] Desilylation of (31) and (32) was achieved in quantitative yield using TBAF in THF to give (33) and (34), respectively Both the silylated and desilylated compounds are air-stable crystalline solids which may be purified by flash chromatography The original chiral centre thus serves effectively to create a further centre at the phosphorus atom Although this method provides an excellent method for the preparation of the required enantiomerically pure heterocycle phosphine unit (33) it has not proved possible to alkylate this molecule to give the target diphosphine donors, or precursors thereof [21] This is due to the low reactivity of the anion of (33), which reacts only with powerful electrophiles



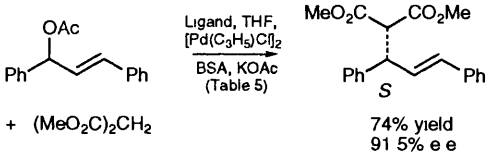
Scheme 9 *Reagents and conditions* i, Bu^{n}Li, TMEDA, ii, PhP(O)Cl$_2$, iii, HSiCl$_3$, Et$_3$N, iv, BH$_3$, v, TBAF

In a more successful sequence, borane-protected mixed phosphorus/nitrogen donor ligands (35) and (36) were prepared by the sequence shown in Scheme 10 from a diamine precursor [20] A 1 1 diastereoisomeric mixture was obtained by this route which was resolved by flash chromatography on silica gel An *X*-ray crystal structure analysis on the less polar isomer (35) confirmed the *trans*-relationship between methyl and phenyl in the compound [22] Evidence for the configurational stability of the ligands was provided by treatment of (35) with an excess of morpholine in THF at reflux which is known to remove the borane, followed by removal of amine under vacuum and addition of excess borane Ligand (35) was recovered in quantitative yield as a single distereoisomer [22]

Encouraged by the recent promising reports on the use of mixed phosphine/nitrogen ligands we envisaged the application of compounds (35) and (36) to the asymmetric catalysis of palladium-catalysed allylic substitution (Scheme 11) *via* an



Scheme 10 *Reagents and conditions* i, 2 2 equiv Bu^{n}Li, 1 1 equiv TMEDA, ether, r t , 16h, ii, 1 5 equiv PhPCl$_2$, − 70 °C, 1h then r t 2h, iii, 4 2 equiv H$_3$B SMe$_2$, r t 1h



Scheme 11

electronically biased palladium-allyl intermediate Our initial speculation was that of the two intermediate complexes formed, *i e* (37) or (38) [illustrated for the ligand derived from the *cis*-isomer (36) in Figure 9], the latter would be destabilized by an unfavourable steric interaction of the ligand phenyl ring with the proximal phenyl ring of the substrate Assuming that the former complex, in which there is an uncongested stacking interaction between the phenyl rings, the well documented *trans*-effect of the nitrogen and phosphorus donors would result in a difference in the positive electron density at each end of the allylic system This would be highest *trans*- to the phosphorus atom since this is a superior π-acceptor Addition of a nucleophile selectively to the allylic terminus indicated in Figure 9 [*i e* to give product of *R*-configuration using the *trans*-isomer (35) and *S* using the *cis*-isomer (36)] would thus generate an enantiomerically pure product [20]

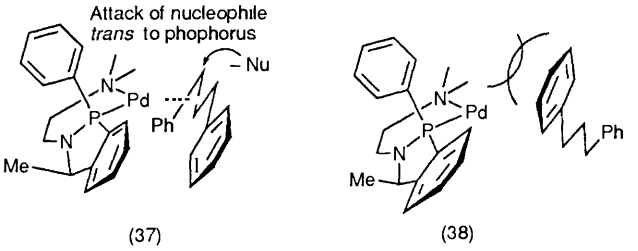


Figure 9 Favoured diastereoisomer (37) of Pd–allyl complex Disfavoured diastereoisomer (38) of Pd–allyl complex

Using an *in situ* method for the removal of borane by morpholine developed in our group we have found that each ligand will indeed accelerate the palladium-catalysed reaction and generate an asymmetric induction (Table 5) Furthermore the observed induction was in the sense predicted by the model in Figure 9 However the level of induction was very low Most remarkably the use of DABCO for the removal of the borane in the preparation of the catalyst from (35) resulted in reversal of the selectivity It occurred to us that the reason for this might be the replacement of the amine part of the ligand in the complex by residual DABCO, resulting in stereocontrol by only the phosphorus part of the ligand To test the viability of this we

Table 5 Palladium-catalysed allylic substitutions of Scheme 11

Ligand	X[a]	Y[b]	Deboration[c]	Yield	ee
(35)	4	10	M	86%	60% (*R*)
(36)	4	10	M	35%	33% (*S*)
(35)	4	10	D	99%	62% (*S*)
(31)	4	20	M	56%	91 5% (*S*)
(31)	4	20	D	31%	89% (*S*)
(31)	1	5	M	84%	84% (*S*)
(31)	1	5	D	56%	85% (*S*)

[a] X refers to mol% Pd *i e* if X = 4 mol% $[(C_3H_5)PdCl]_2$ = 2 [b] mol% ligand M = morpholine D = DABCO

employed the monomeric phosphorus reagent (31) as a catalyst and found that it was superior to the previous compounds, generating an e e of up to 91 5% (at the 20 mol% ligand/5% Pd level) Gratifyingly, however, the e e was still high (84—85%) at the 5 mol% ligand/1% Pd levels [20] At the lower level of ligand and palladium the yield was higher and in the same sense using either deboration method as achieved with (35), which is of the same configuration at phosphorus as (31), and DABCO deprotection (Table 5) The substitution reactions were complete in a few hours at room temperature, suggesting a rate similar to that observed with other mixed nitrogen/phosphorus ligands and superior to that achieved with complexes containing no phosphorus ligand The substitution reaction using the desilylated ligand (33) gave an essentially racemic product after a very short reaction time [22] This result suggests that monomeric phosphine (31) adopts a conformation unlike that of the phosphorus/nitrogen mixed donors (35) and (36) and that the bulky silyl group is essential

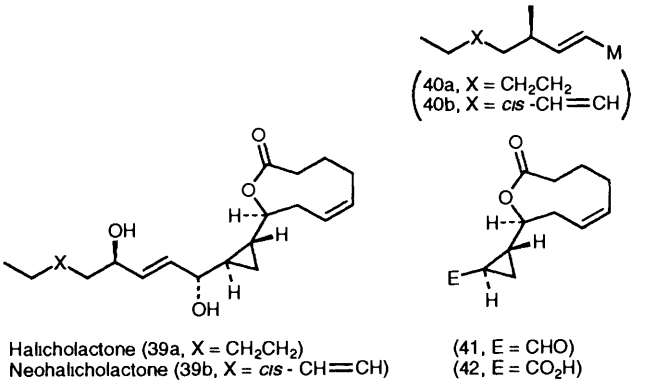
4 Asymmetric Synthesis from Enantiomerically Pure Starting Materials

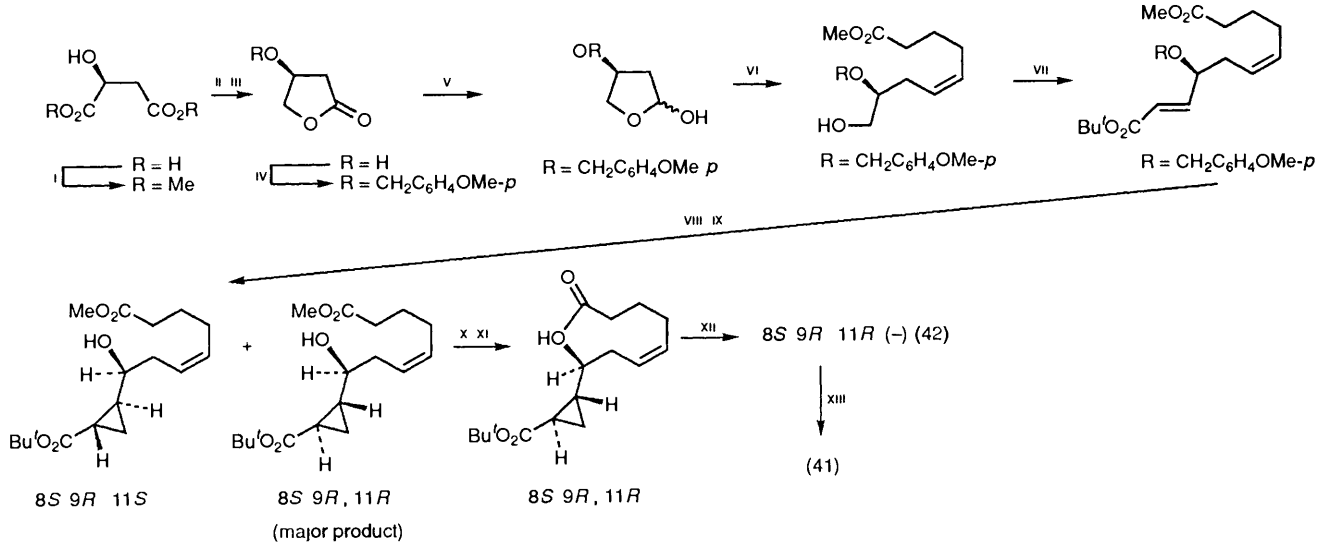
The marine metabolites halichcholactone (39a) and neohalichcholactone (39b), both weak lipoxygenase inhibitors, were isolated from the sponge *Halichondria okadai* and first reported in 1989 [23] As well as acting as lipoxygenase inhibitors, these compounds also contain a number of unusual structural features, including a nine-membered lactone, cyclopropane ring, five chiral centres, and two or three double bonds

Our proposed synthesis of the target molecules involves a convergent route in which the reaction of a vinylic anion (40a) or (40b) with a common aldehyde (41) was a key step As will be demonstrated below, these two fragments are available from each enantiomer of commercially available malic acid (*i e* from the 'chiral pool')

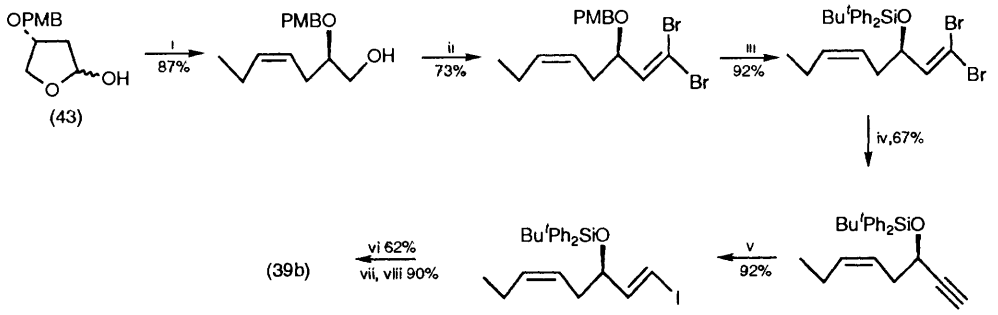
The synthesis of the aldehyde (41) has been reported and is illustrated in Scheme 12 [25] Critical to the success of the synthesis were modifications of conditions of the Wittig reaction which introduced the *cis*-double bond and the use of the Yamaguchi protocol for the lactonization [26] The introduction of the cyclopropane group was achieved using a sulfur ylid following the precedent set by Stork for the diastereoselective control of additions to *trans*-α,β-unsaturated γ-alkoxy esters [27] An *X*-ray crystallographic analysis of the intermediate acid (42) showed the correct relative stereochemistry for the target molecule The structure adopts a very similar conformation to the corresponding region of neohalichcholactone itself

In the case of neohalichcholactone synthesis the control of diastereoselectivity in the late stage coupling steps between vinylic anion (40) (prepared from *R*-malic acid derivative (43) by the route shown in Scheme 13) and (41) was of some concern This is because the *trans*-cyclopropane ring results in orientation of the substituent away from the aldehyde and it is therefore unable to exert any stereochemical control over the addition It is essential therefore that the vinyl anion component is able to direct the addition to some extent In the event we found that it was essential to use a *t*-butyldiphenylsilyl group on the oxygen

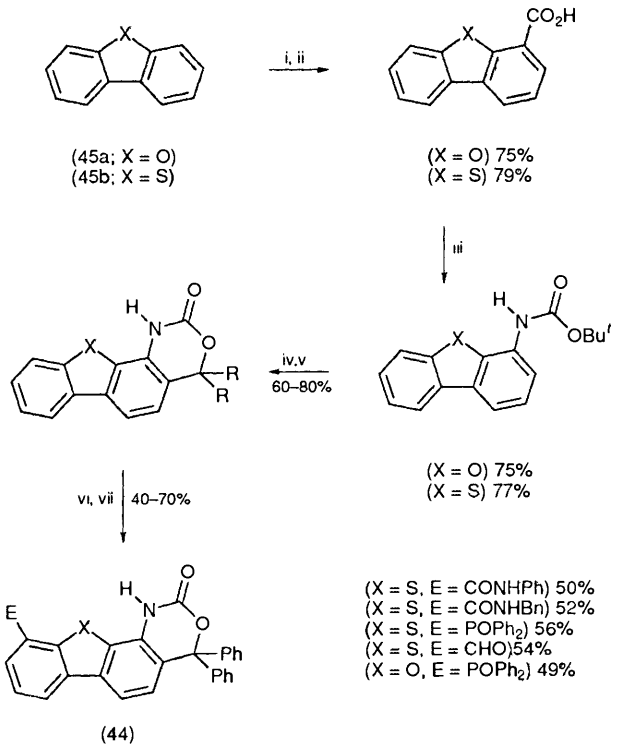




Scheme 12 *Reagents and conditions* i, MeOH, AcOH, 74%, ii, BH_3SMe_2, $NaBH_4$, THF, 92%, iii, TFA, CH_2Cl_2, 80%, iv, $Cl_3CCNHOCH_2C_6H_4OMe$-*p*, cat F_3CSO_3H, 73%, v, DIBAL-H, toluene, −20 °C, 84%, vi, $HO_2C(CH_2)_4PPh_3Br$, NaHMDS, then AcCl, MeOH, 69%, vii, Swern oxidation, then $Bu^tO_2CCH_2PO(OEt)_2$, DBU, LiCl, 66%, viii, $Me_3S(O)I$, NaH, DMSO, 74%, ix, DDQ, CH_2Cl_2 H_2O 18 1, 93%, x, LiOH, THF–MeOH–H_2O 4 1 1, 100% xi, Yamaguchi lactonization,[12] 67%, iii, TFA, CH_2Cl_2, 100%, xiii, $ClCO_2Et$, $NaBH_4$, 90%



Scheme 13 *Reagents and conditions*: i, 1.1 equiv. propylphosphonium bromide, 1.05 equiv. $NaN(SiMe_3)_2$, toluene, r.t. then add ylide to lactol in toluene, − 78 °C to 0 °C; ii, (a) Swern oxidation, 100% crude: (b) 2 equiv. CBr_4, 4 equiv. PPh_3, 8 equiv. Et_3N, CH_2Cl_2, r.t. then 1.0 equiv. crude aldehyde, 0 °C, CH_2Cl_2, 73%; iii, (a) 1.1 equiv. DDQ. 18:1 CH_2Cl_2:H_2O, (b) 1.2 equiv. TBDPSCl, 2.5 equiv. imidazole, DMF; iv, 2.2 equiv. Bu^{n}Li, THF, − 78 °C to r.t.; v, 1.2 equiv. $Cp_{12}ZrHCl$. 1.2 equiv. I_2, THF, r.t.; vi, 1.0 equiv. (46), 3.0 equiv. 6.0 equiv. $CrCl_2$, cat. $NiCl_2$, DMSO/DMF (1:1), r.t.; vii, separation of major isomer by f.c.; viii, 3.0 equiv. TBAF, THF, reflux, 2.5h.



Scheme 14 *Reagents and conditions*: i, Bu^{n}L; [1.0 equiv. for (45a) and 2.0 equiv. for (45b)], THF, 3h, r.t.; ii, solid CO_2, ether; iii, $(PhO)_2P(O)N_3$, Bu^{t}OH, toluene, 5h, 100 °C; iv, Bu^{t}Li, (2.0 equiv.), ether, 2h, 0 °C; v, R_2CO or DMF, ether, − 78 °C; vi, Bu^{t}Li (3.0 equiv.), TMEDA, ether, 3h, − 20 °C → r.t.; vii, electrophile, ether, − 78 °C → r.t.

atom to get any control, in which case it was only 2:1. The chromium(II)/nickel(II) protocol[27] is an excellent method for the reaction in this synthesis, and furnishes the required isomer as the major product. The completion of the synthesis is also shown in Scheme 13.[28] Another interesting observation was the remarkable slow desilylation reaction in the final step.

This work represents the first total synthesis of these two target molecules. All spectroscopic data of our product matched exactly that of authentic material and our rotation confirmed for the first time the absolute configuration of (39b) which had previously been a matter of speculation.

5 Asymmetric Compounds by Resolution

A recently initiated project in the group is to synthesize host molecules of general structure (44), capable of exhibiting hydrogen bonding interactions with protected amino acids.[29] Our expectation is that this class of host would be amenable to chiral modification to generate an enantioselective resolving agent. To prepare these compounds we required a procedure for the sequential elaboration of a rigid heterocyclic spacer unit such as dibenzofuran (45a) or dibenzothiophene (45b). This project is still at a preliminary stage. However our approach to the target host molecules, which required the development of novel *ortho*-lithiation methodology, is shown in Scheme 14. At each stage a different directing group controls the position at which the next substituent is introduced.

The development of this versatile procedure for the controlled introduction of key functional groups onto a rigid heterocyclic spacer unit should provide useful receptors for use in molecular recognition studies, the results of which will be published in due course.

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6 References

1 For recent reviews see, 'The Chemistry of Sulfones and Sulfoxides', S. Patai, Z. Rappaport, and C. J. M. Stirling, Wiley Interscience, 1988.
2 M. Wills, R. J. Butlin, I. D. Linney, and R. W. Gibson, *J. Chem. Soc., Perkin Trans. 1*, 1991, 3383.
3 M. Wills, R. J. Butlin, and I. D. Linney, *Tetrahedron Lett.*, 1992, **33**, 5427.
4 R. J. Butlin, I. D. Linney, D. J. Critcher, M. F. Mahon, K. C. Molloy, and M. Wills, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1581.
5 D. A. Evans, M. M. Faul, L. Columbo, J. J. Bisaha, J. Clardy, and D. Cherry, *J. Am. Chem. Soc.*, 1992, **114**, 5977.
6 I. D. Linney, H. Tye, M. Wills, and R. J. Butlin, *Tetrahedron Lett.*, 1994, **35**, 1785.
7 W. Oppolzer and R. N. Radinov, *J. Am. Chem. Soc.*, 1993, **115**, 1593.
8 D. R. J. Hose, T. Raynham, and M. Wills, *Tetrahedron: Asymmetry*, 1993, **4**, 2159.
9 D. R. J. Hose, T. Raynham, and M. Wills, *Tetrahedron Lett.*, 1994, **35**, 5303.
10 'The Asymmetric Reduction of Ketones', M. Wills and J. R. Studley, *Chem. Ind.*, 1994, 552.
11 For reviews see: (*a*) S. Wallbaum and J. Martens, *Tetrahedron, Asymmetry*, 1992, **3**, 1475. (*b*) D. J. Mathre, A. S. Thompson, A. W. Douglas, K. Hoogsteen, J. D. Carroll, E. G. Corley, and E. J. J.

Grabowski, *J Org Chem*, 1993, **58**, 2880, and references therein
12 B Burns, J R Studley, and M Wills, *Tetrahedron Lett*, 1993 **34**, 7105
13 B Burns, N P King, J R Studley, H Tye, and M Wills, *Tetrahedron Asymmetry*, 1994, **5**, 801
14 For best results the use of a dilute solution of the reagents in dichloromethane with excess (2—3 eq) of triethylamine is recommended
15 (*a*) D Barr, W Clegg, R E Mulvey, and R Snaith, *J Chem Soc Chem Commun*, 1984, 79 (*b*) S E Denmark and R L Dorow, *J Am Chem Soc*, 1990, **112**, 864 (*c*) S E Denmark, P C Miller, and S R Wilson, *J Am Chem Soc*, 1991, **113**, 1468
16 Molecular modelling was carried out by Lynda Linney, a student of Dr I H Williams
17 M Palmer, J R Studley, and M Wills, unpublished results
18 (*a*) K Wetterlin, *J Med Chem*, 1972, **15**, 1182 (*b*) D Hartley and D Middlemiss, *J Med Chem*, 1971, **14**, 895 (*c*) G Breipohol R Geiger S Henke, H-W Kleeman, J Knolle, D Ruppert, B A Scholkens, H Urbach, A Wagner, and H Wegmann, 'Topics in Medicinal Chemistry', Abstracts of the 4th SCI-RSC International Conference on Medicinal Chemistry, published by the Royal Society of Chemistry, pp 101—313
19 B Burns, E Merifield, M F Mahon, K C Molloy, and M Wills, *J Chem Soc Perkin Trans 1*, 1993, 2245
20 G Brenchley, E Merifield, M Wills, and M Fedouloff, *Tetrahedron Lett*, 1994, **35**, 2791
21 Although alkylation with activated electrophiles was possible, a very large number of unsuccessful attempts at this dimerization were made Electrophiles included 1,2- and 1,3- diiodo, dibromo, and ditrifluoromethanesulfonyl ethane, 3-hydroxypropylbromide, and 1,2-ethanediolsulfate Bases included sodium hydride (with and without crown ethers), potassium hydride, butyllithium, and LDA No trace of product was found in any case
22 G Brenchley and M Wills, unpublished results
23 (*a*) H Niwa, K Wakamatsu, and K Yamada, *Tetrahedron Lett*, 1989, **30**, 4543 (*b*) H Kigoshi, H Niwa, K Yamada, T J Stout and J Clardy, *Tetrahedron Lett*, 1991, **32**, 2427
24 D J Cricher S C Connolly, M F Mahon, and M Wills, *J Chem Soc Chem Commun*, 1995, 139
25 J Inanaya, K Hirata, H Saeki, T Katsuki, and T Yamaguchi, *Bull Chem Soc Jpn*, 1979 **52**, 1989
26 G Stork and M Kahn, *Tetrahedron Lett*, 1983, **24**, 3951
27 (*a*) H Jin, J Uenishi, W S Christ, and Y Kishi, *J Am Chem Soc*, 1986, **108**, 5644 (*b*) K Takai, M Tagashira, T Kuroda, K Oshima, K Utimoto, and H Nozaki, *J Am Chem Soc*, 1986, **108**, 6048
28 D Critcher S Connolly and M Wills *Tetrahedron Lett* 1995, **36**, 3763
29 C Eldred, H Tye, and M Wills, *Synlett*, in press