REVIEW

The Sharpless asymmetric aminohydroxylation

Jennifer A. Bodkin and Malcolm D. McLeod *

School of Chemistry, University of Sydney, NSW 2006, Australia

Received (in Cambridge, UK) 16th August 2002
First published as an Advance Article on the web 21st November 2002

Covering: up to 28th February 2002

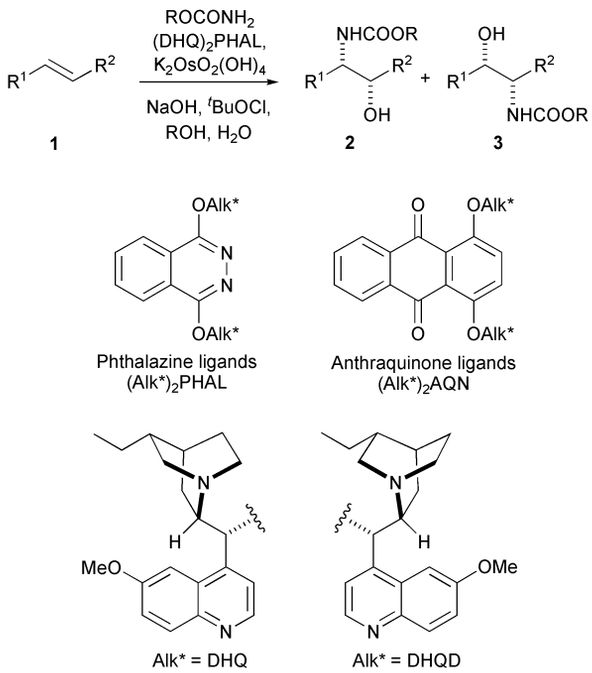
1 Introduction

The Sharpless asymmetric aminohydroxylation (AA), first reported in 1996,[1] allows for the catalytic and enantioselective synthesis of protected vicinal aminoalcohols, in a single step, from a wide range of simple alkene starting materials. The significance of this invention was immediately apparent to many researchers,[2] as the AA reaction provides straightforward access to the aminoalcohol array present in a wide variety of biologically active agents and natural products.[3] As a result, the reaction rapidly gained the prominence of its forerunners, the asymmetric epoxidation (AE)[4] and asymmetric dihydroxylation (AD)[5] processes, and belongs to the significant body of work developed by Sharpless for which he was awarded the 2001 Nobel Prize in Chemistry.

The reaction, typified by the conversion shown in Scheme 1, employs a catalyst consisting of *Cinchona* alkaloid derived ligands and an osmium species in combination with a stoichiometric nitrogen source that also functions as the oxidant. A wide range of nitrogen sources are available that differ in the *N*-substituent and therefore give rise to differently protected aminoalcohol products, most of which correspond to commonly used and synthetically useful protecting groups, such as *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), and 2-(trimethylsilyl)ethoxycarbonyl (Teoc).

The chiral ligands give rise to the observed enantioselectivity by favouring addition to one enantiotopic face of the prochiral alkene substrate. In this way, the 1,4-bis(9-*O*-dihydroquininyl)-phthalazine [$(DHQ)_2PHAL$] ligand directs addition to the α-face of an alkene **1** to form aminoalcohol products such as **2** or **3** (Scheme 1). Alternatively the 1,4-bis(9-*O*-dihydroquinidinyl)-phthalazine [$(DHQD)_2PHAL$] ligand directs addition to the β-face of **1**. The sense of asymmetric induction closely parallels that observed in the AD reaction, suggesting that the factors governing the enantioselectivity of both processes are similar.

An additional complexity that is not manifest in the AD process involves the regioselectivity of the AA reaction. The oxidation of unsymmetrical alkenes such as **1** ($R^1 \neq R^2$) can, in principle, give rise to two regioisomeric aminoalcohol products



Scheme 1

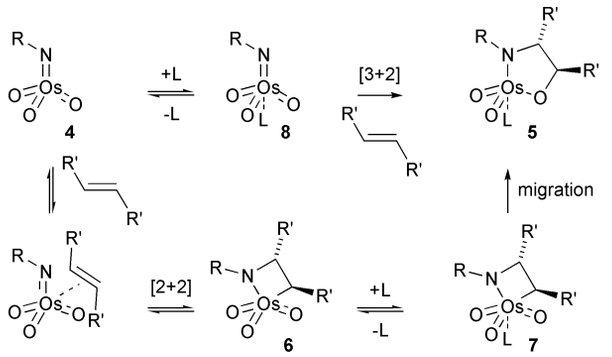
2 and **3**. In many cases, the reaction conditions or the aromatic linker of the chiral ligand, for example phthalazine (PHAL) or anthraquinone (AQN), strongly influence the regioselectivity of the reaction.[6] As will be seen in the following discussion, the control of regioselectivity is often the greatest challenge in the application of the Sharpless AA reaction to synthesis. It is noteworthy that despite the enormous potential of the transformation, relatively few research groups have developed synthetic strategies that rely on the AA reaction as a key step. For the most part, this can be attributed to the problem of controlling the regioselectivity and enantioselectivity of the AA reaction for complex substrates. Effective strategies for addressing this challenge will open numerous new avenues for the efficient synthesis of aminoalcohol-containing compounds.

This review surveys recent developments in this emerging technology and highlights successful strategies for the application of the AA reaction in synthesis. The Sharpless AA reaction has been reviewed previously;[2,3,7–9] however, recent findings justify this update. This review covers the literature up to the end of February, 2002.

2 Mechanism

Proposals for the mechanism of the AA process have been closely based on mechanistic studies of its forerunner, the AD reaction. The intermediate implicated in the key bond forming step is the imidotrioxoosmium(VIII) species **4**, which adds with *syn*-stereospecificity to the alkene to give the azaglycolate

DOI: 10.1039/b111276g



Scheme 2

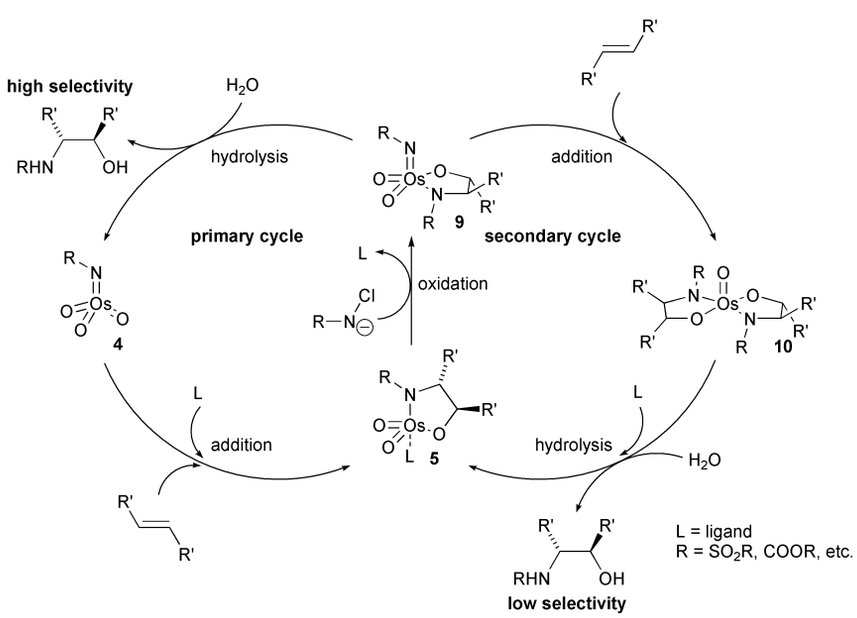
complex **5** (Scheme 2). Two pathways have been suggested for this process, both of which address the preference of **4** to effect aminohydroxylation rather than dihydroxylation, and other key aspects such as enantio- and regio-selectivity.

The proposal advanced by Sharpless[7] parallels that put forward for the AD reaction[10] and involves a formal [2 + 2] cycloaddition of the alkene to the imidotrioxoosmium species **4** to give the osmaazetidine **6**, followed by ligand coordination to form **7** and 1,2-migration of the carbon–osmium bond to give the osmium azaglycolate addition product **5**. This mechanism uses electronic arguments to account for the frequently observed preference for the nitrogen to add regioselectively to the β-carbon of alkenes bearing an electron withdrawing group.[7] The beneficial effects of the ligand on the enantio- and regio-selectivity of the AA reaction occur by influencing the position of the equilibrium (thereby favouring one of the diastereomeric complexes represented by **7**) or by controlling the relative rate of final bond migration to give **5**.[11]

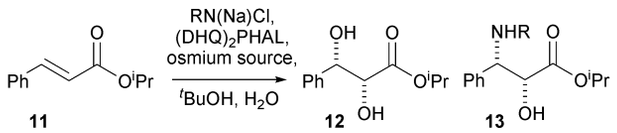
The second mechanistic proposal[12] is the [3 + 2] cycloaddition of ligand-bound complex **8** to the alkene, analogous to the Criegee mechanism for osmium-mediated dihydroxylation.[13] In this instance, catalyst–substrate interactions control the selectivity of the addition.

Considerable debate[9] has surrounded the mechanistically related osmium-mediated dihydroxylation reaction, however, a number of recent findings, including those involving kinetic isotope effects[14] and theoretical calculations,[14,15] lend weight to the [3 + 2] mechanism for this process. This precedent aside, the mechanistic pathway for the crucial bond-forming step associated with the AA reaction requires further investigation. Irrespective of the exact mode of addition, the ligand is observed to increase the rate, influence regioselectivity and induce excellent enantioselectivity in the AA reaction. To account for these observations, a mechanistic scheme has been proposed in which two catalytic cycles, each giving different results for selectivity of the transformation, compete to form products.[7,16,17] The primary cycle is mediated by the alkaloid derived ligand and in all but one of the of the AA methods reported to date,[1] the ligand is observed to improve catalytic turnover relative to the non-ligand-mediated reaction. Ligand-mediated addition of imidotrioxoosmium(VIII) species **4** to the alkene gives azaglycolate species **5** (Scheme 3). Reoxidation of **5** by the nitrogen source gives **9**, which can undergo hydrolysis to regenerate the initial osmium species, **4** and liberate product (hydrolysis of **5** followed by oxidation to **4** is another plausible pathway). The oxidised azaglycolate species **9** may also enter the secondary cycle and add to a second alkene to give the bis(azaglycolate)osmium species **10**. The addition step of this cycle is independent of the *Cinchona* alkaloid derived ligand and, as a result, gives addition products with low enantio- and regio-selectivity. Hydrolysis of **10** leads back to **5**, which can then re-enter either the primary or secondary cycle. The turnover-limiting step in both catalytic cycles is the hydrolysis of azaglycolate complexes **9** or **10**.[17] Control of the oxidation pathway is achieved by conducting the reaction in aqueous solvent mixtures, thereby favouring hydrolysis of **9** and dominance of the primary cycle.[7,16] In the case of the AD reaction, elimination of the secondary cycle was most effectively accomplished by conducting the reaction in biphasic aqueous–organic reaction media.[5] In comparison, all of the AA processes reported to date have been carried out under homogeneous conditions and suppression of the secondary cycle relies on effective hydrolysis of **9**.

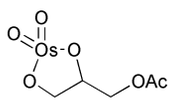
Although Scheme 3 does not explicitly address their formation, diol by-products are frequently observed in the AA reaction. Production of diol reduces chemical yield and can complicate the purification of aminoalcohol products. Lohray and co-workers[18] have reported an investigation into diol formation. Their initial experiments implicated osmium(VIII) species such as osmium tetroxide as a source of diol contaminant. For example, reaction of **11** with stoichiometric osmium tetroxide and chloramine salt afforded a near quantitative yield of diol **12** and no aminoalcohol **13** (Scheme 4). In contrast, the reaction with 10 mol% osmium tetroxide catalyst, afforded a 14:86 ratio of diol to aminoalcohol. In both reactions, the diol **12** was produced with the same sense of stereoinduction as the aminoalcohol product **13** and with high levels



Scheme 3



R	Osmium source (mol%)	12:13	Ee of 12 (%)	Ee of 13 (%)
Ts	OsO_4 (100)	>99:1	98	-
Ts	OsO_4 (10)	14:86	82	90
Ms	OsO_4 (10)	14:86	95	94
Ms	**14** (10)	7:93	not reported	>97



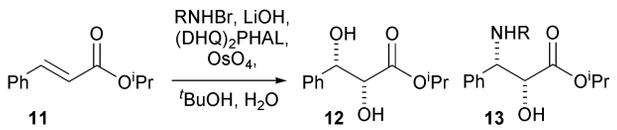
14

Scheme 4

of enantioselectivity (80–95% ee), consistent with a ligand-mediated AD reaction.[5] This result suggests that osmium(VIII) tetroxide undergoes an initial ligand-mediated asymmetric dihydroxylation (AD) reaction to form an osmium(VI) glycolate complex analogous to **5**, which can then enter the AA catalytic cycle upon reoxidation by the chloramine salt followed by hydrolysis to generate the imidotrioxoosmium(VIII) species **4**.

A reduction in diol formation could be achieved by the use of osmium(VI) glycolate complex **14** (Scheme 4) as the initial osmium source, which requires chloramine oxidation and hydrolysis to form the catalytically active osmium(VIII) species **4**. However, the use of **14** did not totally suppress diol formation, suggesting that a second pathway is available to give the diol products. The authors did not report the use of the standard osmium(VI) source recommended for the AA reaction; *viz* potassium osmate dihydrate.

In a separate series of experiments, the influence of electron withdrawing groups was investigated for a range of *N*-bromoacetamides as the nitrogen source. In general, the introduction of halogen substituents gave lower conversion, an increase in the relative proportion of diol **12** to aminoalcohol product **13**, and lower enantioselectivity (Scheme 5). To account for the



R	Recovered 11 (%)	Yield 12 (%)	Yield 13 (%)
CH_3CO	-	11	81
CH_2ClCO	8	30	20
$CHCl_2CO$	53	9	9
CCl_3CO	60	20	-

R	Concentration of 11 (g ml^{-1})	12:13
CH_3CO	0.014	5:95
CH_3CO	0.050	45:55
CH_3CO	0.050 ($AcNH_2$ 1 eq.)	5:95

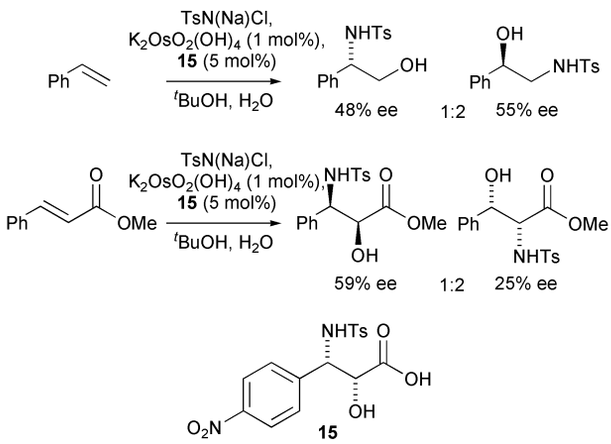
Scheme 5

observed increase in diol formation, the authors proposed that hydrolysis of imidoosmium species such as **4** or **9** to form osmium tetroxide was occurring. A related hydrolysis of imidoosmium species has also been suggested by Sharpless to account for greater levels of diol formation in the AA of styrenes with *tert*-butyl carbamate.[19] Minimisation of this side reaction was achieved by the use of 2 : 1 propanol–water solvent mixtures, with the reduction in water content from the 1 : 1 ratio typical of other AA variants thereby slowing the offending hydrolysis step.

A detailed study of the mechanism of the *N*-bromoacetamide-mediated AA reaction was undertaken as part of the process chemistry optimisation for the large-scale production of the Taxol® sidechain. The researchers involved noted a strong correlation between increasing substrate concentration and the quantity of diol produced (Scheme 5).[20] Diol formation at high concentrations was reduced by the addition of one equivalent of acetamide;[20,21] however the mechanistic underpinnings of this improvement were not fully elucidated. The beneficial effect of this modification of the AA procedure has not been demonstrated to date for other variants involving the chloramine salts derived from sulfonamides or carbamates.

A number of general recommendations may be made with respect to reducing diol formation during AA reactions. Use of the recommended osmium(VI) pre-catalyst, potassium osmate(VI) dihydrate, should minimise the amount of diol by-product. Where the application of osmium(VIII) tetroxide is advantageous,[22] catalyst loadings of *ca.* 4 mol% should be used to limit the diol produced from this source. Reducing the proportion of water in the reaction medium has been demonstrated to decrease diol formation in a number of studies.[19,23] However, this must be balanced against the need for high water concentrations to speed the hydrolysis of osmium azaglycolate intermediates such as **9**.[16] Substrate concentration is another important variable in some AA reactions.[20] Finally, in one instance, the application of high ligand to osmium ratios and slow addition of osmium has been reported to decrease diol formation.[24]

Sharpless has reported the development of asymmetric oxidation procedures that capitalise on the secondary cycle. This innovation stems from the observation that the aminohydroxylation of unsaturated carboxylate salts,[25] amides[26] and some esters,[27] affords racemic product even in the presence of excess ligand, an observation consistent with reaction within the secondary cycle. The extension of this work led to the development of chiral aminoalcohol ligands such as **15**, which bear a carboxylic acid functional group and mediate the new aminohydroxylation or dihydroxylation process (Scheme 6).[25,28]



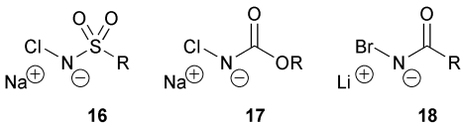
Scheme 6

Aminohydroxylation with the new catalyst proceeded with poor regioselectivity and moderate to low enantioselectivity, clearly illustrating the deleterious effects of the secondary cycle on AA selectivity. Significantly, this secondary cycle aminohydroxylation was more efficient than the alkaloid ligand-mediated reaction in that it proceeded with lower catalyst loadings and without diol formation. Whilst the procedure does not yet represent a useful alternative to the original AA, it is an enticing avenue for future development.

3 Nitrogen sources

There are three main classes of nitrogen source that have been used to date in the AA reaction: the *N*-halogenated species derived from (i) sulfonamides, (ii) carbamates and (iii) amides.

All are converted into the respective alkali metal salt **16**–**18** prior to addition to the alkene (Fig. 1). Optimised reaction conditions specific to each class have been developed and for a detailed discussion of these results the reader is referred to the review by Kolb and Sharpless.[7] More recently, various alternative nitrogen sources have been investigated, such as nitrogen heterocycles.[29,30]



16 **17** **18**

Fig. 1

The sulfonamide method was the first to be developed, stemming directly from the use of chloramine-T [TsN(Na)Cl] in the catalytic but non-asymmetric forerunner to the AA.[31] Chloramine-T remains the most frequently used reagent, due to its low cost and commercial availability. Chloramine-M [MsN(Na)Cl] is the most common alternative, but must be prepared independently or *in situ*.[16] Chloramine-M generally gives higher yields, as well as enantio- and regio-selectivities than chloramine-T, with this superiority thought to be due to the smaller substituent on sulfur.[16,32] This trend is illustrated in Fig. 2 for the major AA products, **19**, derived from methyl cinnamate.

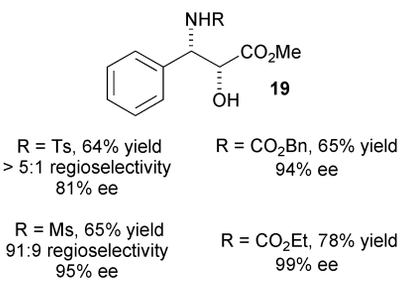
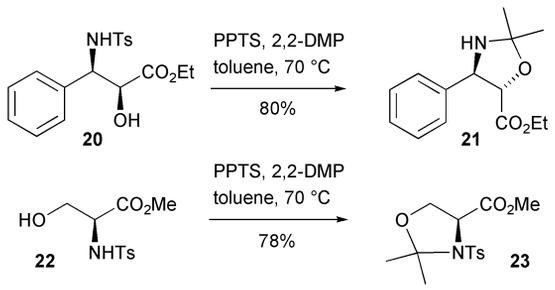


Fig. 2

The most common reaction conditions involve 3 mol equiv. of the chloramine salt in a 1:1 acetonitrile–water or alcohol–water solvent system, although the nitrogen source has also been used in large excess (6 mol equiv.)[33] in order to maximize product yield. The optimal solvent system depends on both the substrate and chloramine used. Chloramine-T in aqueous propanol has been found to give lower yields and higher enantioselectivity than in acetonitrile,[34] and chloramine-M was more successful in propanol despite a slower reaction rate.[16] In alcohol–water mixtures, both chloramine-T and -M frequently afford crystalline AA products, thereby simplifying isolation and allowing enrichment in product ee by recrystallisation.[16]

The robust nature of the sulfonamide products gives rise to the major drawback of this method: harsh deprotection conditions are usually required to generate the free amine.[35,36] The development of milder deprotection methods[37] still has not provided a procedure suitable for use with all AA products. It was discovered that concomitant removal of the tosyl group with 2,2-dimethyl-1,3-oxazolidine formation using 2,2-dimethoxypropane (2,2-DMP) occurred on several AA products containing adjacent ester functionality, such as **20** giving **21** (Scheme 7). However, this deprotection was not universal with all substrates of this type, for example **22** afforded **23**, nor was it observed with aminohydroxylated styrenes.[38]

A number of alternative sulfonamide nitrogen sources have been investigated, including the chloramine salts of *p*-nitrophenylsulfonamide [NsN(Na)Cl],[39] *tert*-butylsulfonamide [BusN(Na)Cl][39] and 2-(trimethylsilyl)ethylsulfonamide.[16] Amines protected as the *p*-nitrophenylsulfonamide derivative



Scheme 7

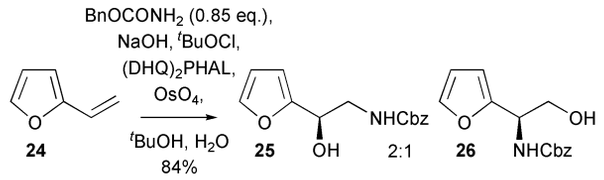
can be unmasked under very mild conditions,[40] but the relevant chloramine reagent is unreliable in the AA reaction.[39] The *tert*-butylsulfonamide-derived chloramine salt [BusN(Na)Cl], the preparation of which has been described in detail,[39] was successfully employed in the racemic aminohydroxylation[26] of a range of αβ-unsaturated amides to afford high yields of aminoalcohols.[39] The 2-(trimethylsilyl)ethylsulfonamide-derived chloramine salt was reported to be comparable to chloramine-M in terms of reactivity.[16] Both these nitrogen sources afford protected amines that can be unmasked under mild conditions.[41]

Another significant drawback of the sulfonamide method is its limited substrate scope, encompassing α,β-unsaturated esters, phosphonates and amides, as well as some terminal and trisubstituted alkenes, but excluding alkenes such as styrenes and vinyl arenes. One notable exception is the successful aminohydroxylation reaction of styrene using stoichiometric chloramine-T and catalytic quantities of **15** as the ligand (Scheme 6).[28]

The discovery of carbamate-based nitrogen sources[32] greatly expanded the scope of the AA reaction to include many styrenes and terminal alkenes. This, coupled with the facile deprotection of carbamates under mild conditions,[42] gave the AA much greater synthetic utility than was the case using the original sulfonamide-based approach. The commonly used carbamates include ethyl, benzyl, *tert*-butyl and 2-(trimethylsilyl)ethyl carbamate (Teoc). All except Teoc are commercially available, and all can be used without purification. In one case, however, the purity of benzyl carbamate was found to be of critical importance, with its recrystallisation increasing the AA yield from 33% to 78%.[43] The carbamate is typically converted, *in situ*, into the corresponding chloramine salt by reaction with sodium hydroxide and 3 mol equiv. of *tert*-butyl hypochlorite.[32] However, owing to the unsuitability of *tert*-butyl hypochlorite for use on a large scale, two viable alternatives have recently been developed: 1,3-dichloro-5,5-dimethylhydantoin and dichloroisocyanuric acid sodium salt.[44] Neither oxidant was found to have an adverse effect on the yield or selectivity of the AA, and both are commercially available, have good shelf stability and act efficiently; only 1.5 mol equiv. are required since both chlorines are available for oxidation.[44]

One frequently encountered difficulty with the carbamate variant of the AA is the removal of unreacted carbamate from the reaction mixture, with extensive column chromatography often being required.[8,23,45] This problem was decreased in the AA of vinylfuran **24**, where use of benzyl carbamate as the limiting reagent was reported to give comparable selectivity and yield of **25** and **26**, to the standard 3 mol equiv. previously employed with this substrate (Scheme 8).[46]

The best solvent system for the carbamate variant of the AA depends on both the substrate and the carbamate used. In most cases, 1:1 propanol–water gives the best results, although in the case of *tert*-butyl carbamate, 2:1 propanol–water is desirable to minimize the amount of diol by-product formed.[19] In cases where substrate solubility was poor, addition of a small amount of DMF,[47] ether[48] or other co-solvent[49] has allowed for successful aminohydroxylation. Mixtures of 1:1 acetonitrile–water

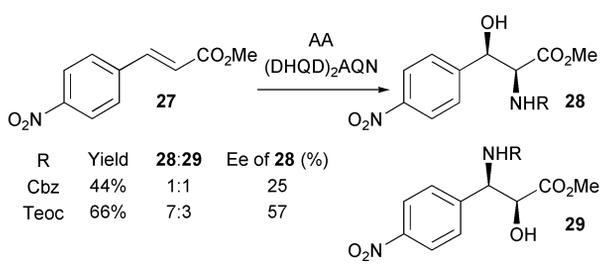


Scheme 8

have been observed to decrease or even to reverse the regioselectivity of the carbamate-based AA.[19]

As with sulfonamides, carbamates with less sterically demanding *N*-substituents were found to give better results. For the AA products, **19**, derived from methyl cinnamate, increased yield and selectivity was achieved using ethyl rather than benzyl carbamate (Fig. 2).[32] However, the relative difficulty of deprotecting ethyl carbamate makes it less synthetically useful than the other variants.

The relative merits of benzyl and *tert*-butyl carbamate appear to vary depending on the AA substrate. With a range of substituted styrene substrates, slight reductions in product yield using *tert*-butyl carbamate were generally obtained, but this was compensated for in higher enantio- and regio-selectivities.[19] There have also been cases of *tert*-butyl carbamate effecting conversion where benzyl carbamate has failed.[23,45,49] The 2-(trimethylsilyl)ethyl reagent generally gives the best yields and selectivities of all the carbamates, also providing the fastest reaction rate which has allowed for the use of reduced osmium catalyst loadings (2 mol% rather than the usual 4 mol%).[50] Its superiority over the benzyl analogue was exemplified by the AA of *p*-nitrocinnamate **27** using $(DHQD)_2AQN$, which gave products **28** and **29** with improved regioselectivity and ee for the desired isomer **28** (Scheme 9).[51] The Teoc protecting group is readily removed with mild acid or fluoride sources.[50,52]



Scheme 9

The most recent major variant of the AA reaction is based on *N*-halogenated amides.[53] This variant is comparable in scope to the carbamate-based method and works well with cinnamates, acrylates, styrenes and terminal alkenes. It is advantageous in that only one equivalent of the *N*-haloamide is required, greatly simplifying isolation of the AA products. As alkali metal salts of *N*-chlorocarbamides are susceptible to Hofmann rearrangement,[54] the lithium salt of commercially available *N*-bromoacetamide was found to be the most viable alternative. By carrying out the reaction at 4 °C, complete suppression of the Hofmann rearrangement was achieved.[53]

Comparison between the $(DHQ)_2PHAL$-mediated AA of isopropyl cinnamate with either 2-(trimethylsilyl)ethyl carbamate[50] in propanol–water or *N*-bromoacetamide[53] in *tert*-butyl alcohol–water illustrates the similarity of these two nitrogen sources (Fig. 3). Both produced excellent enantio- and regioselectivities of their respective major AA products **13**, with the amide procedure affording a higher yield. In formation of AA products **30** (Fig. 3), *N*-bromoacetamide was found to be superior to *tert*-butyl carbamate not only in terms of yield and regioselectivity, but also in terms of the ease of chromatographic separation of the two regioisomers.[55] However, *N*-bromoacetamide has not been found to be a universally

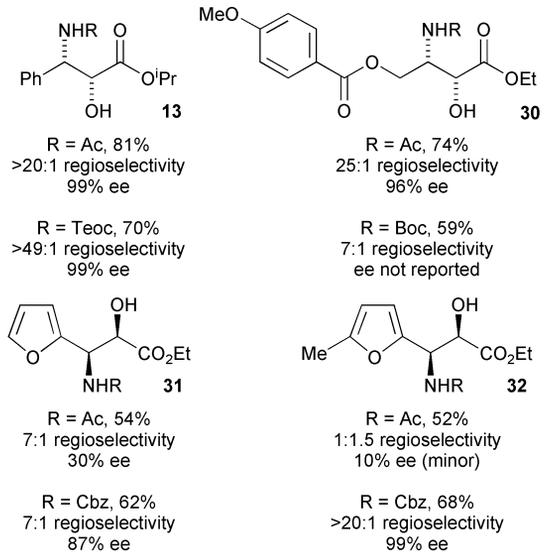
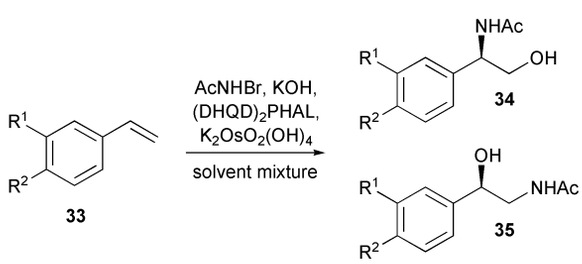


Fig. 3

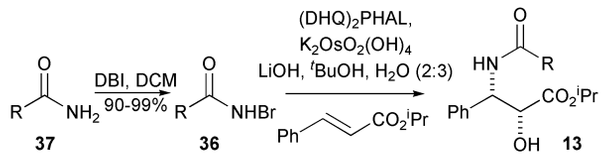
superior reagent; the AA of several furanyl acrylates with benzyl carbamate gave significantly better results than with the amide (**31** and **32**, Fig. 3).[56]

The amide variant has been carried out in either alcohol–water or acetonitrile–water solvent mixtures. Amides show a greater tendency than carbamates to give the benzylic alcohol regioisomer in the AA of styrene substrates **33**, with the choice of solvent system profoundly affecting this tendency. In alcohol–water solvent systems, poor regioselectivities are observed in favour of the protected benzyl amine, whereas in acetonitrile–water the regioselectivity is reversed.[53] This reversal can be further magnified by the selection of anthraquinone ligands (see Section 8). Yields were found to be higher in propanol–water than in the acetonitrile system and in the cases reported,[53] the ee of the benzylic amines **34** (85–91% ee) was higher than that of the regioisomers **35** (62–88% ee) when phthalazine ligands were employed (Scheme 10).



Scheme 10

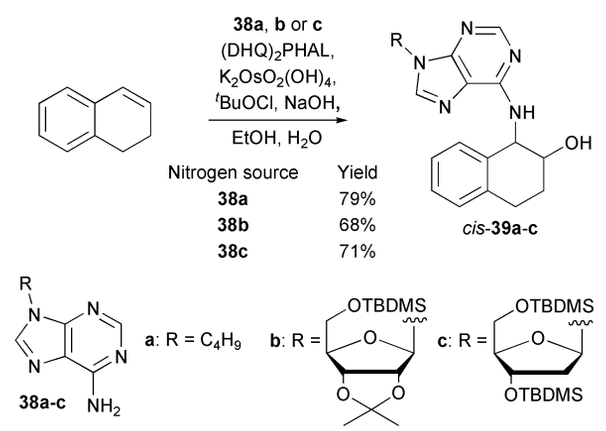
The scope of the amide-based AA was greatly increased with development of a facile monobromination method for primary amides,[21] since only *N*-bromoacetamide is commercially available. The high yielding preparation of several *N*-bromoamides **36** from the parent compounds **37** using dibromoisocyanuric acid (DBI) resulted in observation of the same trend as for the sulfonamides and carbamates, *viz*. the AA reaction gave better results with less sterically demanding substituents on the nitrogen (Scheme 11).[21] Aliphatic amides gave the highest yields, enantio- and regio-selectivities of AA product **13**. Electron-deficient amides and aromatic amides gave poorer outcomes.[21,57]



R	Yield (regioselectivity)	Ee of **13** (%)
Pr	94% (21:1)	95
CH_2Cl	75% (23:1)	95
Ph	38% (2.0:1)	77

Scheme 11

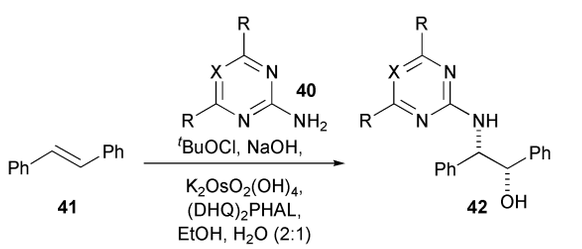
A number of heterocyclic nitrogen sources have been investigated in the aminohydroxylation reaction.[29,58] The AA reaction was attempted using adenine derivatives **38a**–**c** as the nitrogen source[58] and good yields of *cis*-aminohydroxylated products **39a**–**c** were achieved. However, the products obtained were racemic (**39a**) or consisted of a 1 : 1 mixture of tetrahydronaphthalene diastereomers (**39b**,**c**). Clearly, no asymmetric induction from the chiral ligand or the ribose substituents, for **38b** and **38c**, was operative in these transformations (Scheme 12). The reaction has been applied to the efficient synthesis of adenosine conjugates of polycyclic aromatic hydrocarbon metabolites, which are of interest in the study of carcinogenesis.[29]



Nitrogen source	Yield
38a	79%
38b	68%
38c	71%

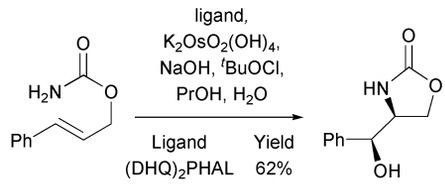
Scheme 12

Although the adenine nitrogen sources did not give rise to asymmetric induction, they provided the platform for subsequent success using nitrogen-substituted heterocycles such as **40**.[30] Thus, using an optimised 2 : 1 ethanol–water solvent system, stilbene **41** was converted into either enantiomer of the aminoalcohols **42** (Scheme 13) with good to excellent yields and enantioselectivities.



Scheme 13

A tethered carbamate, **43**, was utilized by Donohoe and coworkers[59] in a bid to control the regioselectivity of the AA for allylic alcohol substrates. This approach gave complete regioselectivity for the formation of oxazolidinone **44**, but no enantioselectivity was observed in the presence of chiral ligand $(DHQ)_2PHAL$ despite the observation of improved turnover (Scheme 14). Hünig's base was also found to



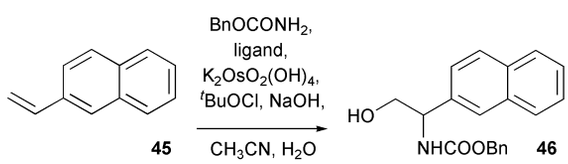
Ligand	Yield
$(DHQ)_2PHAL$	62%
$^iPr_2NEt$	59%
quinuclidine	26%
none	42%

Scheme 14

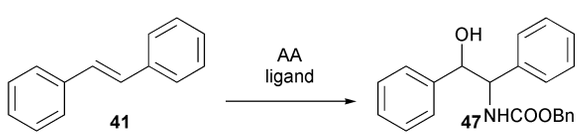
accelerate the reaction, while quinuclidine was not an efficient promoter.[59]

4 Enantioselectivity

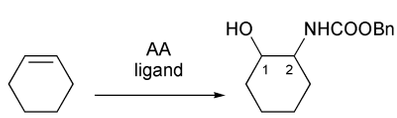
The sense of enantioselectivity in the AA reaction is predictable, but its magnitude is highly dependent on the alkene substitution pattern. As a general rule, asymmetric induction is of the same sense and similar magnitude to that of the AD reaction for related substrates. In this respect, the AD mnemonic proposed by Sharpless[5] as well as other models[60] may be used in a predictive manner. A few examples should serve to illustrate this point. The AA reaction of monosubstituted alkenes such as 2-vinylnaphthalene **45** favours formation of the benzylic amine **46** with greater than 10:1 regioselectivity.[32] Use of the $(DHQD)_2PHAL$ ligand favours production of the (*R*)-enantiomer **46** in 99% ee, whilst the AD reaction on the same substrate has been reported to afford the (*R*)-diol in 98% ee.[5] Application of the pseudoenantiomeric $(DHQ)_2PHAL$ ligand affords the (*S*)-enantiomer of **46** in 99% ee (Scheme 15).



Ligand	Stereoisomer	Ee (%)
$(DHQ)_2PHAL$	*S*	99
$(DHQD)_2PHAL$	*R*	99



Ligand	Stereoisomer	Ee (%)
$(DHQ)_2PHAL$	*S*,*S*	91
$(DHQD)_2PHAL$	*R*,*R*	88



Ligand	Stereoisomer	Ee (%)
$(DHQ)_2PHAL$	1*S*,2*R*	63
$(DHQD)_2PHAL$	1*R*,2*S*	56

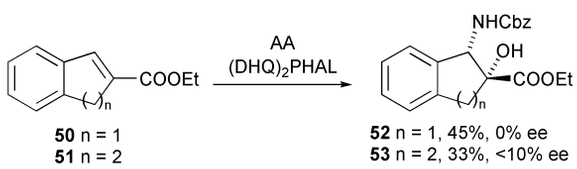
Scheme 15

The AA reactions of (*E*)-1,2-disubstituted alkenes also frequently give excellent enantioselectivity. The $(DHQ)_2PHAL$-mediated AA reaction of stilbene **41** affords (*S*,*S*)-**47** with 91% ee[32] whilst the AD reaction on the same substrate has been reported to afford the (*S*,*S*)-diol with >99.5% ee.[5] The AA of **41** with $(DHQD)_2PHAL$ ligand gives (*R*,*R*)-**47** in 88% ee.[32]

Alkenes with (*Z*)-1,2-disubstitution have also been reported to undergo the AA reaction selectively. In the case of symmetrical (*Z*)-alkenes no related precedent exists for the AD

reaction as the diol products formed are achiral. However, the different heteroatoms derived from the AA reaction give rise to non-symmetrical products, which are obtained with moderate enantioselectivity. Cyclohexene **48** affords the AA product (1*S*,2*R*)-**49** with $(DHQ)_2PHAL$ and (1*R*,2*S*)-**49** with $(DHQD)_2PHAL$ in 63 and 56% ee respectively.[32] Few other examples of the AA reaction of (*Z*)-alkenes have been reported to date, with the notable exception of the desymmetrisation of dienylsilanes discussed below (Section 5).[61]

Despite the close correlations outlined above, an important qualification must be made: the literature contains very few examples of the AA of more highly substituted alkenes. Thus, no enantioselective AA reactions have been reported for 1,1-disubstituted, trisubstituted or tetrasubstituted alkenes. In the case of 1,1-disubstitued alkenes, a number of non-asymmetric aminohydroxylations have been reported and it has been suggested that these capitalise on reactivity within the secondary catalytic cycle (Scheme 3).[25–27] Aminohydroxylation reactions of trisubstituted compounds have largely been restricted to examples where other factors such as diastereoselection are also operative.[33] For example, an attempt to extend established AA methodology[36] to conformationally restricted analogues of the Taxol® sidechain involved the reaction of indene **50** and dihydronaphthalene **51** (Scheme 16). Both substrates reacted to



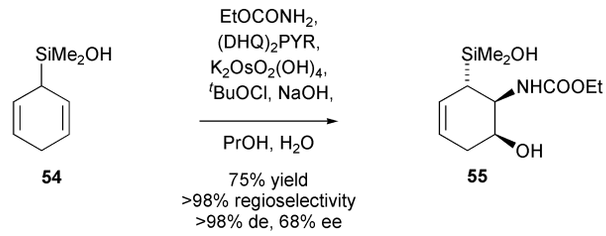
Scheme 16

afford the desired regioisomers **52** and **53** but without appreciable enantioselectivity (0 and <10% ee).[62] Access to the desired compounds was afforded by the successful AD reaction (*ca.* 92% ee) and re-functionalisation of the resulting products.

The more limited tolerance of alkene substitution pattern for the AA as opposed to the AD reaction may be due to the greater steric demand of the reactive imidotrioxoosmium complex **4** relative to osmium tetroxide. The greater size of the imido substituent (Os=NR *vs.* Os=O) would render approach of the nitrogen to a disubstituted olefinic carbon more difficult and, to date, no synthetically useful AA reaction for the production of an amine bearing a fully substituted carbon has been reported. This constraint could also rule out catalyst–substrate binding modes for the AA of more highly substituted alkenes, such as **50** and **51**, that remain viable for the AD reaction and lead to enantioselective dihydroxylation of these substrates. The steric hindrance provided by higher alkene substitution patterns would also influence other aspects of the AA reaction such as regioselectivity (Section 6).

5 Diastereoselectivity

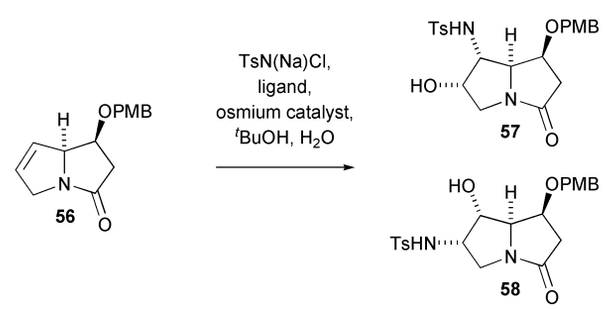
The application of catalytic asymmetric transformations in synthesis invariably leads to situations where induction from stereogenic centres in the substrate must be considered in addition to any influence from the catalyst. A prime example of this interplay between substrate stereochemistry and catalyst is given by the Sharpless kinetic resolution procedure.[4] A number of recent studies have harnessed diastereocontrol of the AA reaction to useful ends in synthesis, the most striking example of this being the desymmetrisation of silyl cyclohexadienes developed by Landais and coworkers.[61,63] In this instance the AA reaction of **54** proceeds with complete diastereoselectivity, favouring addition *anti* to the bulky silyl substituent (Scheme 17). This preference for the less hindered approach was accompanied by a completely regioselective process to afford **55**. In addition, the influence of the PYR ligands favoured addition to



Scheme 17

one enantiotopic double bond to give the product with an ee of 68%. In this remarkable transformation, the high diastereoselectivity of the AA reaction is integral to the selective functionalisation and desymmetrisation of **54**. This product was secured in enantiomerically pure form by a single recrystallisation and has been used as a key building block in the synthesis of aminocyclitols and aminocarbasugars.

High diastereoselectivity in the AA reaction is also a feature of the synthesis of (+)-loline reported by White and coworkers[24] (Scheme 18). The aminohydroxylation of **56** under a

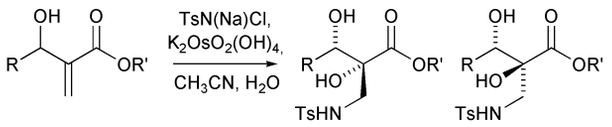


Osmium catalyst (mol%)	Ligand (mol%)	Yield (%) diol	Yield (%) **57** + **58**	**57**:**58**
OsO_4 (5)	none	29	18	85:15
$K_2OsO_2(OH)_4$ (4)	$(DHQ)_2PHAL$ (8)	39	38	65:35
$K_2OsO_2(OH)_4$ (4)	$(DHQD)_2PHAL$ (8)	48	47	80:20
$K_2OsO_2(OH)_4$ (1 x 3)	$(DHQD)_2PHAL$ (25)	21	52	75:25

Scheme 18

range of conditions afforded **57** and **58**, corresponding to approach of the reagent to the less hindered face of the alkene. The original non-asymmetric aminohydroxylation conditions gave the diol as the major product and **57** and **58** as an 85:15 mixture of regioisomers (18%). The introduction of *Cinchona* alkaloid ligands was observed to increase the yield of the desired product and reduce diol formation. Optimised conditions involved portion-wise addition of the osmium catalyst and high concentrations of chiral ligand relative to osmium to give the aminoalcohol products in 52% yield and as a 3:1 mixture of regioisomers. Changing the ligands was observed to have no effect on the diastereoselectivity and only a limited influence on the regioselectivity of the reaction. It is worthwhile noting that a number of unsuccessful attempts to elaborate **56** to (+)-loline *via* oxidation of the alkene had failed and thus the aminohydroxylation chemistry, although modest in terms of yield and selectivity, was instrumental in attaining the target.[24]

Diastereoselection in acyclic systems has been reported for the aminohydroxylation of Baylis–Hillman alkenes such as **59** (Scheme 19).[27] Aminohydroxylation of the racemic substrates **59** gave the regioisomerically pure but racemic tertiary alcohol products **60** and **61**, with the former representing the major diastereomer in all cases examined. Increasing the size of either the allylic substituent or ester group was found to increase diastereoselectivity. It has been proposed that these reactions belong to the special case of ligand-independent aminohydroxylations that proceed with catalytic turnover within the secondary cycle (Scheme 3).[28] Consistent with this proposal, the



59 *rac*-**60** *rac*-**61**

R	R'	Yield (%)	**60**:**61**
Me	Me	88	88:12
Me	^{t}Bu	71	92:8
^{i}Pr	Me	71	98:2

Scheme 19

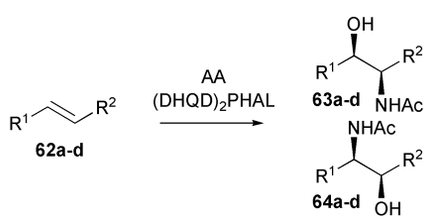
addition of a chiral ligand had no influence on the stereoselectivity of the reaction.

6 Regioselectivity

Control of regioselectivity in the AA is arguably the single greatest challenge when applying the reaction in synthesis. Greater understanding of the factors responsible for controlling regioselectivity would significantly expand the scope of the AA reaction and assist in the development of synthetic strategies that centre on this transformation. The problem of regioselectivity is a complex one and many factors have been invoked to explain observed trends, such as alkene substitution, alkene polarisation and ligand–substrate interactions. Even simple substrates like cinnamate esters, which preferentially give the β-amino ester products, contain a number of features that may influence regioselectivity. Given the data at hand, it is extremely difficult to assess the significance of each proposed influence in isolation. With this qualification in mind, the following discussion aims to assess each of these areas in turn and highlight strategies for the control of AA regiochemistry.

6.1 Alkene substitution

The AA of the homoallylic alcohol derivatives shown in Scheme 20 serve to illustrate the general trend that the nitrogen



62a-d **63a-d** **64a-d**

Substrate	R^1	R^2	**63**:**64**
62a	$TBDPSOCH_2CH_2$	H	>20:1
62b	*p*-MeO-$C_6H_4OCH_2CH_2$	H	1.2:1
62c	$TBDPSOCH_2CH_2$	Et	2.0:1
62d	*p*-MeO-$C_6H_4OCH_2CH_2$	Et	1:3.5

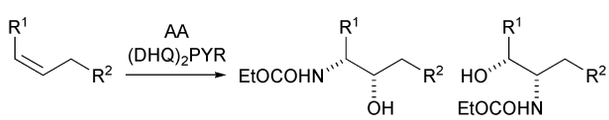
Scheme 20

prefers to add to the less substituted end of the alkene. Both monosubstituted alkene substrates **62a** and **62b** afforded the terminal amine products **63a** and **63b**, respectively, as the major regioisomer. In contrast, the 1,2-disubstituted alkenes **62c** and **62d** give different major regioisomers **63c** and **64d**, respectively, depending on the nature of the protecting group on the homoallylic alcohol. The preference for amination of the less substituted carbon is modest for monosubstituted alkenes and, indeed, there are many examples, such as styrenes, where the amination of the more substituted carbon is preferred. However, the influence of alkene substitution can dominate the reaction, to the point where the aminohydroxylation of 1,1-disubstituted and trisubstituted alkenes give only the less substituted amine products and tetrasubstituted alkenes do not react. These observations may be explained by the greater steric demand of the substituted imidoosmium grouping (Os=NR) relative to the unsubstituted oxo-counterpart (Os=O) in the reactive complex **4** or **8** (Scheme 2), which favours approach of the former to the less substituted olefinic carbon (see Section 4 for further discussion).

6.2 Alkene polarisation

Polarisation of the alkene has been suggested as a contributing influence on the preference of α,β-unsaturated esters to afford the β-amino product with phthalazine derived ligands.[7,11,12] Though the precise rationale varies depending on whether the formal [2 + 2][7,11] or [3 + 2] cycloaddition[12] is invoked as the preferred mechanistic pathway (Scheme 2), it has been suggested that the β-amino isomer predominates due to the greater nucleophilic character of the imidoosmium grouping (Os=NR) relative to (Os=O) which favours addition to the more electrophilic carbon of the alkene. However, changing the aromatic linker of the chiral ligand to an anthraquinone unit results, for a range of α,β-unsaturated esters,[6] in a reversal in regioselectivity such that the α-aminated products are now favoured. This fact speaks against a strong electronic bias.

Electronic directing effects have also been proposed as a controlling influence on regioselectivity in the $(DHQ)_2PYR$-mediated desymmetrisation of dienylsilane **54** (Scheme 17),[63] with nitrogen preferentially adding to more electrophilic carbon of the allylsilane functional group. However, further studies into the AA of acyclic alkenes did not support electronic control. The AA of allylsilane **65a** afforded **66a** as the major regioisomer, favouring addition of the nitrogen to the electron rich olefinic carbon (Scheme 21). Reaction of allylic alcohol



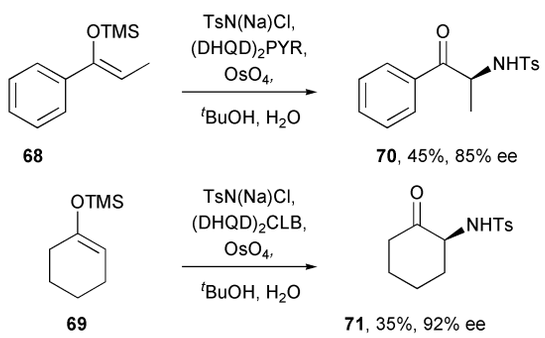
65a-d **66a-d** **67a-d**

Substrate	R^1	R^2	Yield (%)	**66**:**67**
65a	Me	$SiMe_2Ph$	60	75:25
65b	Me	OH	51	50:50
65c	H	$SiMe_2(O^iPr)$	60	100:0
65d	H	OH	83	100:0

Scheme 21

65b gave no regioselectivity. Interestingly, the monosubstituted alkenes **65c** and **65d** both gave the terminal amines as the sole regioisomer, consistent with the dominance of alkene substitution in the control of regiochemistry as outlined above (Section 6.1).

As shown in Scheme 22, the AA of trisubstituted silyl enol



68 **70**, 45%, 85% ee

69 **71**, 35%, 92% ee

Scheme 22

ethers such as **68** and **69** resulted in addition of nitrogen preferentially at the mono-substituted end of the double bond, to afford secondary protected aminoketones **70** and **71** respectively.[64] This is contrary to the expectation that nitrogen adds to the more electron-deficient carbon and this example suggests the dominant influence of alkene substitution in controlling AA regioselectivity. In the light of the evidence assembled above, it appears that alkene polarisation does not exert a major influence on the regioselectivity of the AA reaction.

6.3 Ligand–substrate interactions

The most comprehensive study of ligand–substrate interactions has been reported by Janda and co-workers.[12] They propose a model for the AA reaction with phthalazine derived ligands analogous to that proposed by Corey[60] for the AD reaction. In the putative active complex, the osmium lies at the centre of a distorted trigonal bipyramid composed of equatorial oxygens, with the nitrogens from both the quinuclidine ring and the nitrogen source occupying axial positions[12] (**72**, Fig. 4). Assuming the proposed geometry of the OsO_3N_2 species, the regioselectivity of the AA then arises from the mode in which the alkene binds to the catalyst.[12] It is clear that an unsymmetrically substituted alkene could orient in two different ways with regard to the binding cleft of the catalyst (mode A and mode B, Fig. 4), to produce two different regioisomeric products. It follows that ligand–substrate interactions will be important in determining the mode in which an alkene will approach the catalyst.[65]

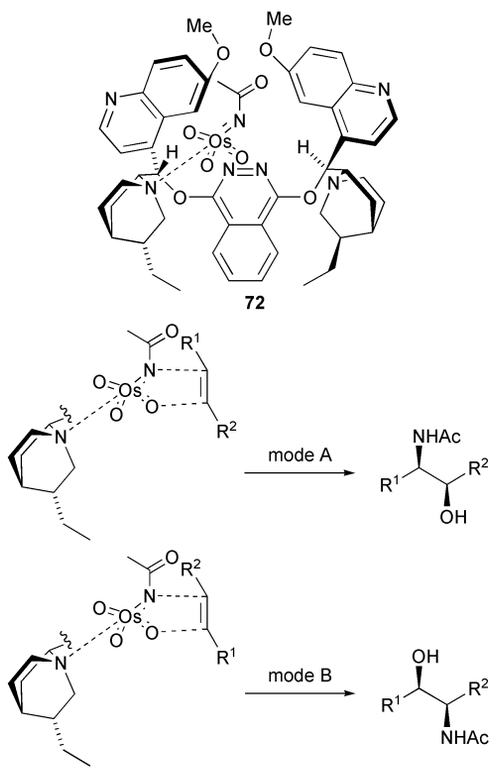
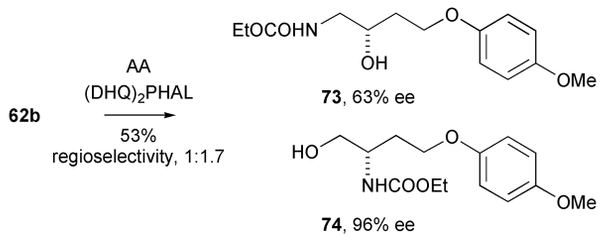


Fig. 4 Proposed structure of the $AcN{=}OsO_3$–$(DHQD)_2PHAL$ catalyst, **72** and alternative alkene binding modes A and B[12]

The effect of modifying the steric demand and ligand binding properties of structurally similar disubstituted alkene substrates is illustrated by the examples in Scheme 20.[12] Protection of the homoallylic alcohol as the bulky silyl ether in **62c** would be expected to favour the AA where the silyl substituent is located outside the narrow binding cleft formed by the methoxyquinoline rings of the ligand (mode B). This would favour the formation of regioisomer **63c** as observed. In contrast, the *p*-methoxyphenyl ether in **62d** can interact favourably with the binding cleft formed by the methoxyquinoline rings (mode A), promoting the formation of the alternative regioisomer **64d**.

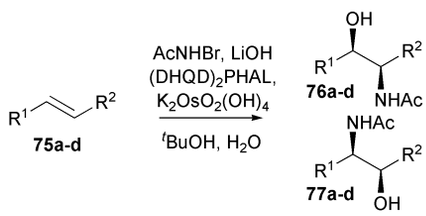
A number of other conclusions may be drawn from the AA of **62b** under the ethyl carbamate conditions, which afforded **74** as the major regioisomer in 96% ee (Scheme 23).[66] The formation of this product corresponds to the binding mode in which the phenyl ether occupies the methoxyquinoline binding cleft (mode A). In contrast, lower selectivity was observed for the minor regioisomer **73** (63% ee) resulting from positioning of the aromatic ether outside the binding cleft in the Janda model



Scheme 23

(mode B). It is clear that substrate–ligand interactions do not only influence regioselectivity but have a profound impact on enantioselectivity as well.

A substrate in which a number of influences on regiochemistry reinforce each other would be anticipated to give high regioselectivity.[12] Substrates **75a** and **75b** (Scheme 24) were designed to favour binding mode B (Fig. 4), with the bulky TBDPS group sterically excluded from the binding cleft, and aryl–aryl interactions favouring binding of the naphthalene within the cleft. This approach gave AA products **76a** and **76b** (>95% ee and 92% ee, respectively) with excellent regiochemical control.[12] The regioselectivity was reversed by interchanging the position of the aromatic moiety in **75c** (relative to **75a**,**b**) favouring binding mode A (Fig. 4) and AA product **77c** (>95% ee).[12]



Substrate	R^1	R^2	**76**:**77**
75a	$TBDPSOCH_2$	CH_2O-2-naphthoyl	>20:1
75b	$TBDPSOCH_2$	CO_2-(2-naphthyl)methyl	17:1
75c	*p*-methoxybenzoyl-OCH_2	CO_2Et	1:25
75d	p-nitrobenzyl-OCH_2	CO_2Et	1:11

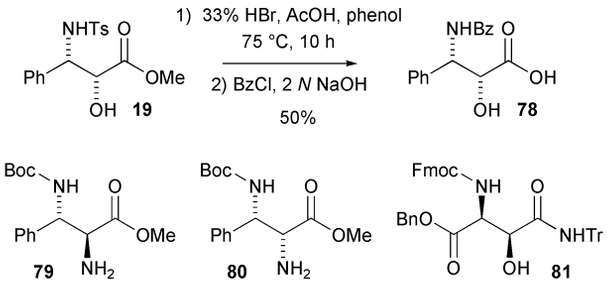
Scheme 24

A detailed study of the influence of substrate structure on regioselectivity has been conducted for aromatic ester derivatives of ethyl 4-hydroxybut-2-enoate,[55] which gave variable regioselectivity (4–25:1). The presence of π-donating substituents on the aromatic ring of the ester was observed to give the best results, with the optimal substrate for the AA reaction being *p*-methoxybenzoyl ester **75c** (Scheme 24). Alternatively, protection of the allylic alcohol as a range of substituted benzyl ethers afforded lower levels of regioselectivity (1.2–11:1) with *p*-nitrobenzyl ether **75d** strongly favouring the formation of **77d** as the major regioisomer. These results point to subtle electronic influences on ligand–substrate interactions. A rationalisation of these results was proposed based on dipole–dipole interactions between the aromatic residues and the methoxyquinoline cleft in binding mode A (Fig. 4).

Ligand–substrate interactions could account, at least in part, for the regioselectivity generally observed in the AA of cinnamates and styrenes (and many other substrates). For both of these alkene types, nitrogen addition at the benzylic position is favoured,[19] consistent with the aromatic group occupying the ligand binding cavity during the alkene addition.

7 Synthetic applications

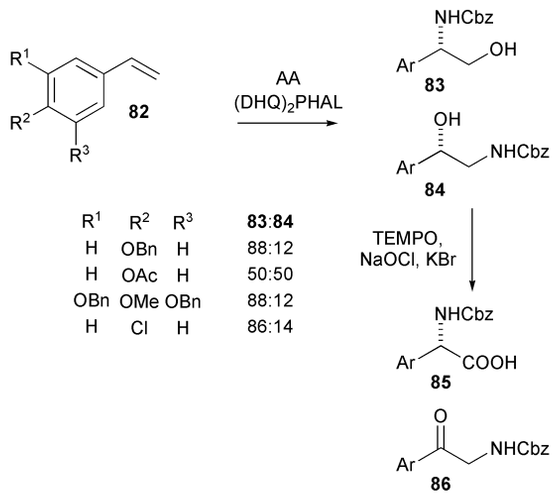
The excellent regioselectivity afforded by cinnamate substrates led to the earliest synthetic application of the AA reaction, a short synthesis of the Taxol® C-13 side-chain **78**. The AA product **19**, (Scheme 25) isolated in high purity by direct crystallisation from the reaction mixture, was elaborated to **78** in two steps.[36] The AA of cinnamate substrates has also provided



Scheme 25

access to 2,3-diamino-3-phenylpropanoic acid derivatives such as **79** and **80**,[67] and has been used in the synthesis of the differentially protected amino acid derivative L-*threo*-β-hydroxyasparagine **81**.[68]

Reliable regioselectivity from styrene AA has been exploited in the synthesis of arylglycines, providing a short, enantioselective route to these important α-amino acids. Central to the widespread adoption of this approach was the study of the AA on a broad range of substituted styrenes **82**, allowing examination of the effect of different aryl substituents on the reaction regioselectivity (Scheme 26).[19] High ee's (*ca.* 90%) were gener-



Scheme 26

ally obtained for the major regioisomer **83**. Subsequent oxidation could be carried out on the crude mixture of regioisomers **83** and **84** using TEMPO to afford the desired α-amino acid **85**, which was easily separated from amino ketone **86** by acid–base extraction.[19]

The efficient, enantioselective preparation of aryl glycines using AA methodology has made this approach attractive in several syntheses. Examples include aminoalcohols **87**, **88**, **89** and **90** (yields and ee's given, Fig. 5), which were oxidized to their respective amino acids on route to syntheses of ristocetin A,[48] the vancomycin CD ring system,[69] conformationally restricted L-arginine analogues,[70] and mesityl-substituted amino acids.[71] Compound **91** was protected as the MEM ether and debenzylated before coupling with **92** to form a biaryl ether in the synthesis of teicoplanin.[43] Similar AA products have been precursors to a wide range of glycopeptide antibiotics.

The regioselectivity of styrene AA has also made this reaction suitable for formation of oxazolidinone chiral auxiliaries.[44,72,73] The AA of vinylnaphthalene **45** allowed isolation of a single regioisomer which was cyclised by treatment with base to **93** (Scheme 27).[72] The AA has also been applied to the synthesis of bis-oxazolines,[74] aminoalcohols[75] and aziridinyl alcohols[76] for application as chiral auxiliaries or ligands. O'Brien has reported a detailed study of the AA reaction of a range of styrene substrates for the synthesis of chiral diamines.[23,45]

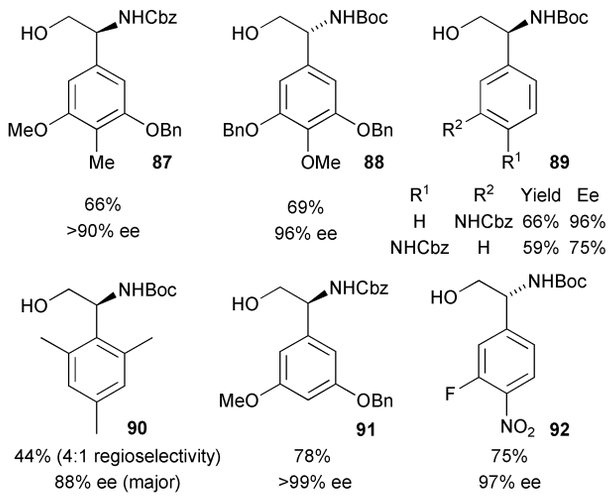
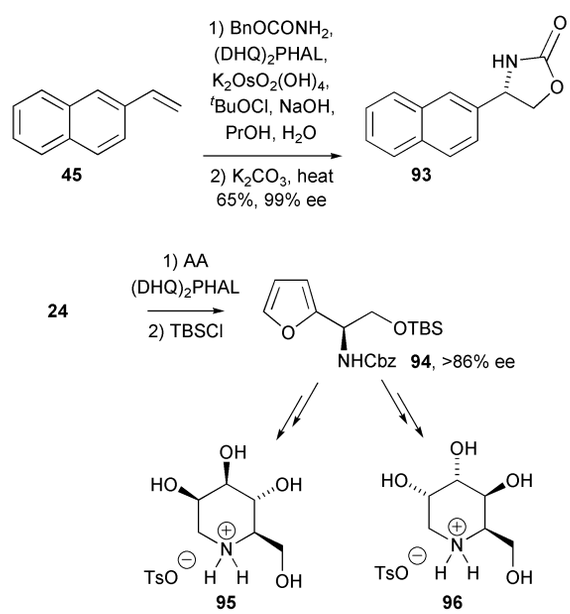


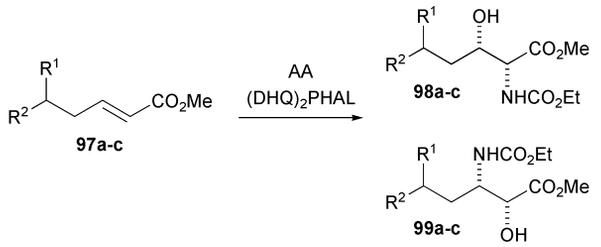
Fig. 5



Scheme 27

The normally high level of regioselectivity attainable with styrene substrates does not extend to the AA of vinylfuran **24**, affording a 2:1 mixture of AA products (Scheme 8). Selective silylation of the primary alcohol allowed ready isolation of the amine **94** (although in low yield), which was converted, by a short sequence, into the deoxymannojirimycin and deoxygulojirimycin derivatives, **95** and **96**, respectively (Scheme 27).[46]

The AA has been used in the synthesis of a wide variety of amino acid derivatives, including the examples of cinnamates (Scheme 25) and styrenes (Scheme 26) given, all of which contain aromatic residues. Application of the AA reaction to a range of aliphatic α,β-unsaturated esters has also been successful in the synthesis of important aminated products. In a study directed towards the synthesis of amino sugars, engineering of AA substrate **97a** allowed improvement of what was initially poor regioselectivity favouring the undesired α-amino isomer **98a** (Scheme 28).[77] Replacement of the dimethyl acetal of **97a** with methyl substituents to give substrate **97b** resulted in reversal of regioselectivity to favour the desired regioisomer **99b** in moderate ee. The selectivity was greatly enhanced upon substitution of the alkyl chain with an aromatic ether to give substrate **97c**. The dramatic improvement in regioselectivity (1:>20) and enantioselectivity (98% ee) observed for **97c** has been proposed to arise through favourable binding interactions between the ligand and the aromatic ether.



Substrate	R^1	R^2	**98**:**99**	Ee of **99** (%)
97a	MeO	MeO	1.3:1	83
97b	Me	Me	1:2.3	60
97c	H	*p*-MeO-C_6H_4O	1:>20	98

Scheme 28

Diaminobutanoic acids **100** and **101** were prepared using the AA,[65,78] as were amino acids **102** and **103** in the syntheses of loracarbef[79] and MetAP-1 inhibitors,[80] respectively (Fig. 6). The

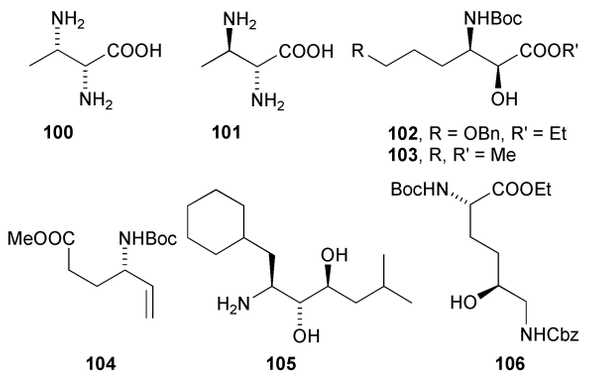
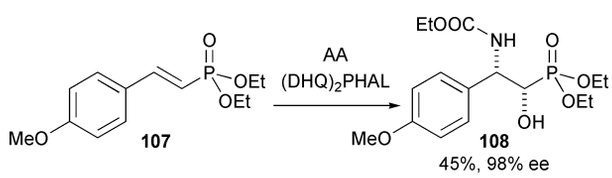


Fig. 6

AA has also been applied to the synthesis of a protected form, **104**, of the anticonvulsive agent vigabatrin,[81] the aminoalcohol components of aspartic protease inhibitors **105**,[82] and hydroxylysine derivative **106**.[83] Such diversity in applications of the AA is illustrative of the enormous value of the process.

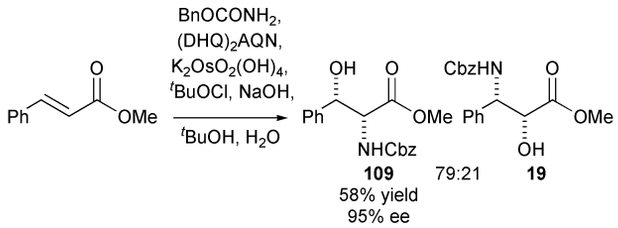
The AA of unsaturated phosphonates by either the sulfonamide[34,84] or carbamate[34] method can be performed in a similar way to unsaturated esters. The best enantioselectivities were obtained with substrates bearing an aromatic substituent in the β-position. For example, AA of **107** afforded β-amino isomer **108** in moderate yield and 98% ee (Scheme 29). Poor asymmetric induction (15% ee) was observed for a vinyl phosphonate.[84]



Scheme 29

8 Reverse regioselectivity

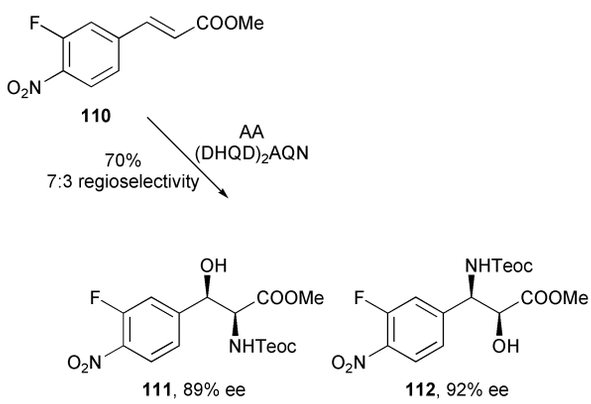
One of the most remarkable aspects of the AA is the observation that different ligands may be used to control the regioselectivity of the transformation. Substitution of the aromatic spacer of the *Cinchona* alkaloid ligands from a phthalazine to an anthraquinone unit (Scheme 1) has been observed to reverse the normal pattern of regioselectivity for a range of substrates.[6] For example, methyl cinnamate undergoes AA with benzyl carbamate as the nitrogen source and $(DHQ)_2AQN$ ligand to afford α-aminoester **109** as the major regioisomer in 58% isolated yield and with an enantiomeric excess of 95% (Scheme 30). Strikingly, this reversal of regioselectivity occurs with no



Scheme 30

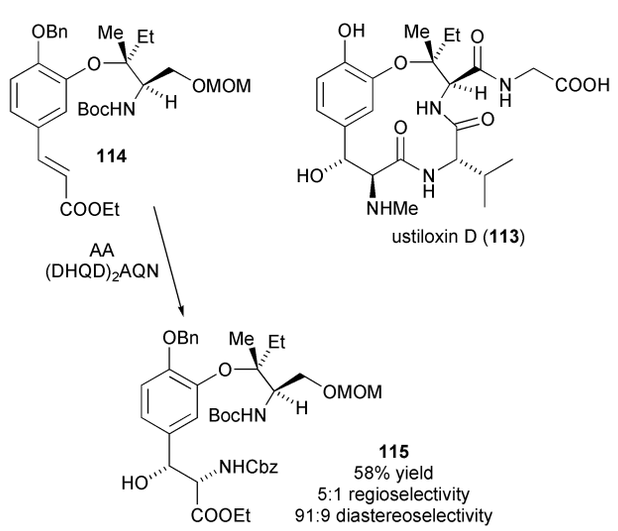
alteration to π-facial selectivity. Indeed, the enantioselectivity of this process is comparable to the $(DHQ)_2PHAL$-mediated reaction,[32] which favours the formation of **19** with an ee of 94% (Fig. 2). The reasons for this dramatic reversal in regioselection have not been elucidated, though it has been proposed that changing the ligand structure favours an alternative substrate orientation with respect to the osmium–ligand complex.[6]

A wide range of cinnamate esters exhibited similar reversal in regioselectivity for AA with anthraquinone ligands, although electron poor substrates such as 3- and 4-nitrocinnamates (Scheme 9) gave poor results.[6,51] Under carefully optimised conditions, the AA of nitrocinnamate **110** with 2-(trimethylsilyl)ethyl carbamate in aqueous propanol gave, in good ee, a 7 : 3 ratio of regioisomers **111** and **112** (Scheme 31).



Scheme 31

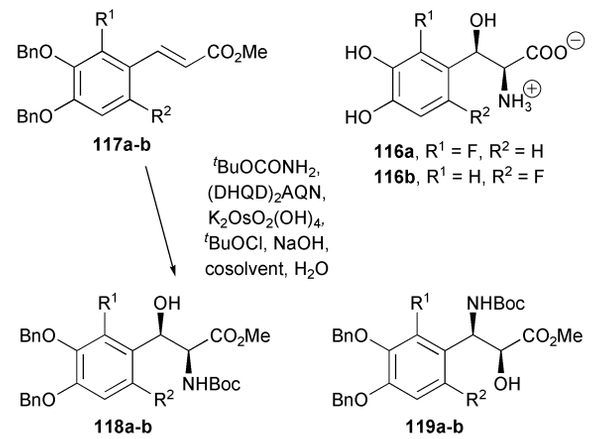
The formation of **111** was exploited in an approach to ustiloxin D (**113**, Scheme 32).[51,85] Specifically, the 3-fluoro-4-nitro aromatic system of **111** was designed as a suitable electrophilic partner to construct the challenging tertiary alkyl aryl ether by nucleophilic aromatic substitution.[51] Faced with the failure of this approach,[85] attention turned to an alternative AA-based synthesis of this key structural unit whereby tertiary alkyl aryl



Scheme 32

ether formation preceded aminohydroxylation. In one of the most complex examples of AA reported to date, the $(DHQD)_2$-AQN-mediated AA reaction of highly functionalised substrate **114** afforded **115** in 58% yield and with good diastereoselectivity as a key step in the first total synthesis of ustiloxin D (Scheme 32).[85]

Another application of the AA in which reversal in regioselectivity was exploited was in the synthesis of fluorinated (2*S*,3*R*)-(dihydroxyphenyl)serine derivatives **116a** and **116b** (Scheme 33), which have been identified as potential precursors



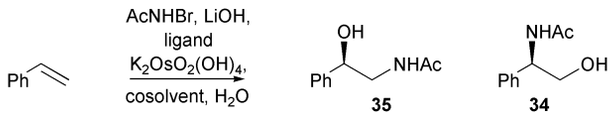
Substrate	R^1	R^2	Cosolvent	Yield (%)	**118**:**119**	Ee of **118** (%)
117a	F	H	PrOH	76	4.5:1	86
117b	H	F	PrOH:CH_3CN (10:1)	36	3.7:1	68

Scheme 33

to selective α- and β-adrenergic receptor antagonists.[49] The researchers investigated the anthraquinone-mediated AA reaction to give direct access to the serine regioisomer, **118**. The 2-fluoro isomer **117a** was found to be a good substrate for the AA reaction and afforded a 76% yield of aminoalcohol products **118a** and **119a**, favouring the serine regioisomer **118a** as the major product in 86% ee. The use of propanol as the cosolvent was found to be critical for the success of this transformation, with acetonitrile and *tert*-butyl alcohol giving inferior yields and enantioselectivities. Elaboration of **118a** to target **116a** was performed by a three-step sequence, which included a recrystallisation to boost the ee to 93%.

Interestingly, the AA of the 6-fluoro isomer **117b** under identical conditions gave a poor yield of aminoalcohol products (24%), together with diol by-product and recovered starting material, demonstrating that minor changes in the substrate can have a profound influence on the AA reaction. Optimisation of the transformation focused on variation of the reaction solvent mixture in an effort to improve substrate solubility. The most synthetically convenient procedure relied on the doubling of reagent quantities and the use of a mixed organic cosolvent to afford **118b**, which was obtained in modest yield and with limited selectivity. Elaboration of **118b** by the same three-step sequence including the recrystallisation of a synthetic intermediate eventually gave **116b** in 95% ee. Despite the moderate levels of selectivity and yield, the AA reaction nevertheless provided a short, synthetically viable route for the large scale production of **116a** and **116b**, supplanting a previous and more lengthy synthetic scheme relying on auxiliary-controlled asymmetric aldol reactions.[86]

Reversal in regioselection through the use of anthraquinone ligands is also observed for styrene substrates, although the results appear less general and solvent is an important variable. Styrene undergoes AA with *N*-bromoacetamide as the nitrogen source and $(DHQ)_2PHAL$ ligands in aqueous propanol to afford the benzylic amine **34** as the major regioisomer in 91% ee (Scheme 34).[53] Aqueous acetonitrile reverses this modest preference to afford **35** as the major product. The application of

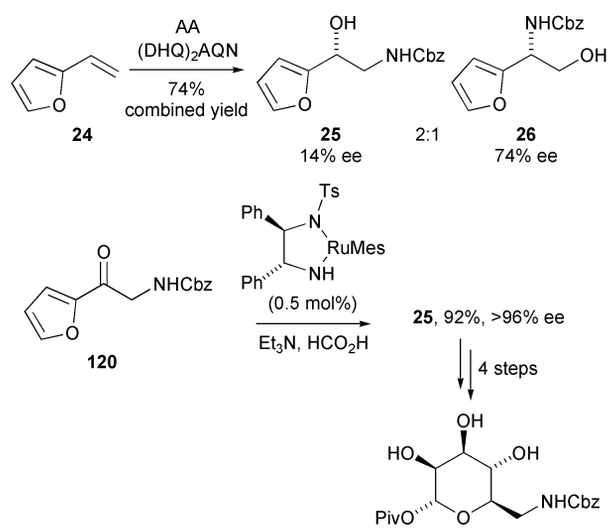


Ligand	Cosolvent	Combined Yield (%)	**35**:**34**	Ee (%) **35**	Ee (%) **34**
$(DHQD)_2PHAL$	PrOH	72	1:1.1	83	91
$(DHQD)_2PHAL$	CH_3CN	55	6.1:1	88	-
$(DHQD)_2AQN$	CH_3CN	36	13:1	88	-

Scheme 34

anthraquinone ligands enhances the preference for formation of the benzylic alcohol, giving a 13:1 ratio of **35** to **34**, albeit in lower yield. A similar study has also been reported for the benzyl carbamate variant of the AA. Although reversal of regioselectivity was observed for the anthraquinone ligand-mediated reaction, the ee values of the major benzylic alcohol products, analogous to **35**, were low (0–80%).[19]

Reverse regioselectivity in the AA of vinylfuran **24** was investigated as an approach to the synthesis of 6-aminosugars.[87] Conducting the reaction with $(DHQ)_2AQN$ ligands in aqueous alcohol solvents afforded a 2:1 mixture of **25** and **26** but the major regioisomer was isolated in low (14%) ee (Scheme 35). An

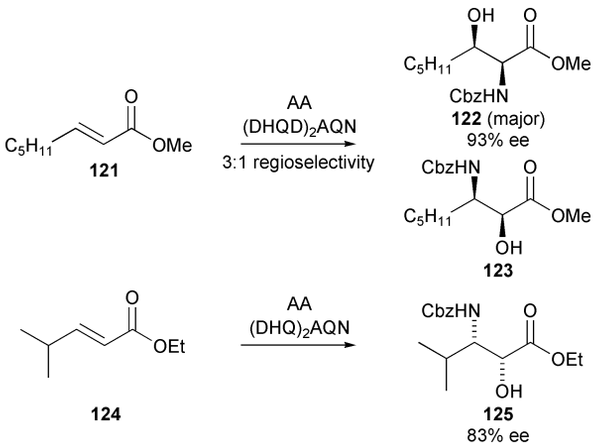


Scheme 35

alternative and highly enantioselective synthesis of **25** was devised, based on the ruthenium-catalysed transfer hydrogenation of a prochiral ketone **120**, which afforded **25** with excellent enantioselectivity and in 92% yield.

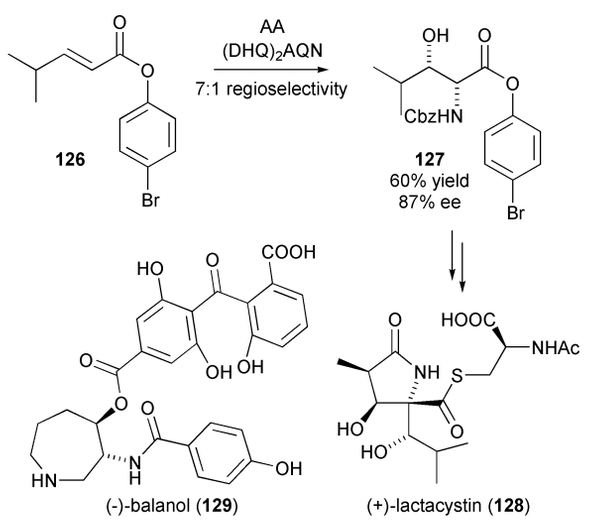
Application of the anthraquinone ligands to the AA of substrates that do not bear an appropriately positioned aromatic moiety are limited and give mixed results. Thus, the $(DHQD)_2$-AQN-mediated AA of methyl (*E*)-oct-2-enoate (**121**) afforded a 3:1 ratio of isomers **122** and **123** with excellent enantioselectivity (Scheme 36).[6] By contrast, $(DHQ)_2AQN$-mediated AA reaction of **124** did not result in reversed regioselectivity and gave the β-amino ester **125** as the sole regioisomer in 83% ee.[22] The dramatic difference in regioselectivity for these two reactions is difficult to rationalise.

Methods leading to the α-aminoester regioisomer for non-cinnamate substrates were investigated by Panek,[22] based on the hypothesis that an appropriately positioned aromatic moiety could influence regioselectivity. The anthraquinone ligand-mediated AA of a range of aryl ester substrates was observed to give the α-aminoester as the major product. Electron donating *p*-substituents gave better regio- and enantio-selectivities with halogen substituents, in particular, giving the highest ee's. Hydrolysis of the aryl esters was a general problem with these substrates but this could be limited by the application of aqueous osmium tetroxide solution as the osmium source and a



Scheme 36

reduction in the amount of aqueous base being used. Applying these optimised conditions to *p*-bromophenyl ester **126** gave 7:1 regioselectivity and a 60% yield of **127** which was obtained in 87% ee (Scheme 37).[22] Hydroxyleucine derivatives such as **127**



Scheme 37

have been used as key synthetic intermediates in a number of syntheses of (+)-lactacystin (**128**) with the result that a number of synthetic strategies have been developed to provide access to this building block.[22,88] The AA based strategy remains among the shortest and most efficient approaches to this structural unit.[88,89] A related approach has been reported for the enantioselective synthesis of the hexahydroazepine core of (−)-balanol (**129**).[22,90]

The regiochemical outcome of the AA of aryl ester substrates such as **126** (Scheme 37) is in marked contrast to that observed for ethyl ester **124** (Scheme 36) and, once again, suggests that ligand–substrate interactions have a profound influence on the regiochemistry of the AA reaction. This study clearly indicates that appropriate substrate design can enhance selectivity of anthraquinone-mediated AA reactions, a concept which closely parallels the studies conducted by Janda for the phthalazine-derived ligands.[12]

9 Solid supported catalysts

Solid-supported catalysts have been investigated in the hope that this modification would provide a simple means of recycling the expensive *Cinchona* alkaloid ligands and osmium used in the AA. Several different solid supports have been investigated,[91,92] with the *Cinchona* alkaloid ligand bound to the support *via* the dihydroquinidine or dihydroquinine moiety. A silica gel supported catalyst is the most successful reported to date, giving comparable results to those observed in the homogeneous AA reaction as applied to cinnamate derivatives and using amide nitrogen sources.[92] Attempts to recycle the catalyst afforded a reduced yield of product (despite the retention of high enantioselectivity), although catalytic activity was restored upon addition of 2 mol% $K_2OsO_2(OH)_4$ to the reaction mixture. This suggests that loss of osmium rather than destruction of the ligand is the main obstacle to recycling the reagent. Attempts to recycle the other catalyst systems also resulted in reduction or loss of activity.[91]

10 Future prospects

Enormous improvements have been made to the AA reaction since the initial disclosure in 1996. The AA of a wide range of alkenes can now be conducted in high yields as well as with excellent enantio- and regio-selectivity. Evaluating the large body of research surrounding the AA gives a clear indication of the optimal conditions for a given substrate and defines the scope of the transformation with respect to factors such as alkene substitution. Clearly the lessons learned from past endeavours will inform those working with the AA in the future but they also present a challenge: can catalytic systems be found to extend the AA to more highly substituted systems?

The development of predictive models that correlate substrate structure with AA regioselectivity must rank among the most important contributions to the field in recent years. The insight provided by these models will give greater confidence in the planning and execution of synthetic sequences that rely on the AA as a key step.

Finally, new paradigms of chemical reactivity are being forged from the AA reaction, such as new catalytic systems based on the secondary cycle and tactics for controlling the regioselectivity using tethered carbamates. Such developments promise much for the future.

11 References

1 G. Li, H.-T. Chang and K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 451.
2 O. Reiser, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1308.
3 S. C. Bergmeier, *Tetrahedron*, 2000, **56**, 2561.
4 Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune and K. B. Sharpless, *J. Am. Chem. Soc.*, 1987, **109**, 5765.
5 H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483.
6 B. Tao, G. Schlingloff and K. B. Sharpless, *Tetrahedron Lett.*, 1998, **39**, 2507.
7 H. C. Kolb and K. B. Sharpless, in *Transition Metals for Organic Synthesis*, eds. M. Beller, C. Bolm, Wiley-VCH, Weinheim, 1998, 2, p. 243.
8 P. O'Brien, *Angew. Chem., Int. Ed.*, 1999, **38**, 326.
9 C. Bolm, J. P. Hildebrand and K. Muniz, in *Catalytic Asymmetric Synthesis*, ed. I. Ojima, Wiley-VCH, New York, 2000, p. 399.
10 D. W. Nelson, A. Gypser, P. T. Ho, H. C. Kolb, T. Kondo, H.-L. Kwong, D. V. McGrath, A. E. Rubin, P.-O. Norrby, K. P. Gable and K. B. Sharpless, *J. Am. Chem. Soc.*, 1997, **119**, 1840.
11 K. B. Sharpless and G. G. Li, *USP* 5 767 304/1997 (*Chem. Abstr.*, **128**, 61 355).
12 H. Han, C.-W. Cho and K. D. Janda, *Chem. Eur. J.*, 1999, **5**, 1565.
13 R. Criegee, *Justus Liebigs Ann. Chem.*, 1936, **522**, 75.
14 A. J. DelMonte, J. Haller, K. N. Houk, K. B. Sharpless, D. A. Singleton, T. Strassner and A. A. Thomas, *J. Am. Chem. Soc.*, 1997, **119**, 9907.
15 (*a*) U. Pidun, C. Boehme and G. Frenking, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2817; (*b*) S. Dapprich, G. Ujaque, F. Maseras, A. Lledos, D. G. Musaev and K. Morokuma, *J. Am. Chem. Soc.*, 1996, **118**, 11660; (*c*) M. Torrent, L. Deng, M. Duran, M. Sola and T. Ziegler, *Organometallics*, 1997, **16**, 13.
16 J. Rudolph, P. C. Sennhenn, C. P. Vlaar and K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2810.
17 K. B. Sharpless and V. V. Fokin, *USP* 6,350,905/2002 (*Chem. Abstr.*, **134**, 178 819).
18 B. B. Lohray, V. Bhushan, G. J. Reddy and A. S. Reddy, *Indian J. Chem., Sect. B*, 2002, **41**, 161.

19 K. L. Reddy and K. B. Sharpless, *J. Am. Chem. Soc.*, 1998, **120**, 1207.
20 P. G. M. Wuts, A. M. Anderson, M. P. Goble, S. E. Mancini and R. J. VanderRoest, *Org. Lett.*, 2000, **2**, 2667.
21 Z. P. Demko, M. Bartsch and K. B. Sharpless, *Org. Lett.*, 2000, **2**, 2221.
22 A. J. Morgan, C. E. Masse and J. S. Panek, *Org. Lett.*, 1999, **1**, 1949.
23 P. O'Brien, S. A. Osborne and D. D. Parker, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2519.
24 (*a*) P. R. Blakemore, S.-K. Kim, V. K. Schulze, J. D. White and A. F. T. Yokochi, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1831; (*b*) P. R. Blakemore, V. K. Schulze and J. D. White, *Chem. Commun.*, 2000, 1263.
25 V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 3455.
26 A. E. Rubin and K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2637.
27 W. Pringle and K. B. Sharpless, *Tetrahedron Lett.*, 1999, **40**, 5151.
28 M. A. Andersson, R. Epple, V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 472 The structures given at the head of tables 2, 3 indicate the relative stereochemistry of the products. In table 2, ligands **4**, **6** give the (2*S*,3*R*), (2*R*,3*S*) stereoisomers, respectively. We thank Professor Fokin for clarifying this issue (V. V. Fokin, personal communication).
29 A. S. Pilcher, H. Yagi and D. M. Jerina, *J. Am. Chem. Soc.*, 1998, **120**, 3520.
30 L. J. Goossen, H. Liu, K. R. Dress and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 1999, **38**, 1080.
31 (*a*) K. B. Sharpless, A. O. Chong and K. Oshima, *J. Org. Chem.*, 1976, **41**, 177; (*b*) E. Herranz and K. B. Sharpless, *J. Org. Chem.*, 1978, **43**, 2544; (*c*) E. Herranz, S. A. Biller and K. B. Sharpless, *J. Am. Chem. Soc.*, 1978, **100**, 3596; (*d*) E. Herranz and K. B. Sharpless, *J. Org. Chem.*, 1980, **45**, 2710.
32 G. Li, H. H. Angert and K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2813.
33 J. S. Clark, R. J. Townsend, A. J. Blake, S. J. Teat and A. Johns, *Tetrahedron Lett.*, 2001, **42**, 3235.
34 A. A. Thomas and K. B. Sharpless, *J. Org. Chem.*, 1999, **64**, 8379.
35 (*a*) S. Ji, L. B. Gortler, A. Waring, A. Battisti, S. Bank, W. D. Closson and P. Wriede, *J. Am. Chem. Soc.*, 1967, **89**, 5311; (*b*) R. C. Roemmele and H. Rapoport, *J. Org. Chem.*, 1988, **53**, 2367.
36 G. Li and K. B. Sharpless, *Acta Chem. Scand.*, 1996, **50**, 649.
37 (*a*) E. Vedejs and S. Lin, *J. Org. Chem*, 1994, **59**, 1602; (*b*) A. F. Parsons and R. M. Pettifer, *Tetrahedron Lett.*, 1996, **37**, 1667; (*c*) B. Nyasse, L. Grehn and U. Ragnarsson, *Chem. Commun.*, 1997, 1017; (*d*) C. Goulaouic-Dubois, A. Guggisberg and M. Hesse, *J. Org. Chem*, 1995, **60**, 5969.
38 S. Chandrasekhar and S. Mohapatra, *Tetrahedron Lett.*, 1998, **39**, 695.
39 A. V. Gontcharov, H. Liu and K. B. Sharpless, *Org. Lett.*, 1999, **1**, 783.
40 T. Fukuyama, C.-K. Jow and M. Cheung, *Tetrahedron Lett.*, 1995, **36**, 6373.
41 (*a*) S. M. Weinreb, D. M. Demko, T. A. Lessen and J. P. Demers, *Tetrahedron Lett.*, 1986, **27**, 2099; (*b*) P. Sun, S. M. Weinreb and M. Shang, *J. Org. Chem.*, 1997, **62**, 8604.
42 T. W. Green and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Wiley & Sons Inc., New York, 2nd edn., 1991.
43 D. L. Boger, S. H. Kim, Y. Mori, J.-H. Weng, O. Rogel, S. L. Castle and J. J. McAtee, *J. Am. Chem. Soc.*, 2001, **123**, 1862.
44 N. S. Barta, D. R. Sidler, K. B. Somerville, S. A. Weissman, R. D. Larsen and P. J. Reider, *Org. Lett.*, 2000, **2**, 2821.
45 P. O'Brien, S. A. Osborne and D. D. Parker, *Tetrahedron Lett.*, 1998, **39**, 4099.
46 (*a*) M. H. Haukaas and G. A. O'Doherty, *Org. Lett.*, 2001, **3**, 401; (*b*) M. L. Bushey, M. H. Haukaas and G. A. O'Doherty, *J. Org. Chem.*, 1999, **64**, 2984.
47 J. Xie and J. M. Valery, *J. Carbohydr. Chem.*, 2001, **20**, 441.
48 A. J. Pearson and J.-N. Heo, *Org. Lett.*, 2000, **2**, 2987.
49 I. H. Kim and K. L. Kirk, *Tetrahedron Lett.*, 2001, **42**, 8401.
50 K. L. Reddy, K. R. Dress and K. B. Sharpless, *Tetrahedron Lett.*, 1998, **39**, 3667.
51 H. Park, B. Cao and M. M. Joullie, *J. Org. Chem.*, 2001, **66**, 7223.
52 L. A. Carpino and J.-H. Tsao, *Chem. Commun.*, 1978, 358.
53 M. Bruncko, G. Schlingloff and K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1483.
54 E. S. Wallis and J. F. Lane, in *Organic Reactions*, ed. R. Adams, Wiley & Sons, Inc, New York, 1946, 3, p. 267.
55 (*a*) C.-Y. Chuang, V. C. Vassar, Z. Ma, R. Geney and I. Ojima, *Chirality*, 2002, **14**, 151; (*b*) C.-Y. Chuang, V. C. Vassar, Z. Ma, R. Geney and I. Ojima, *Chirality*, 2002, **14**, 757 (Erratum).
56 (*a*) H. Zhang, P. Xia and W. Zhou, *Tetrahedron: Asymmetry*, 2000, **11**, 3439; (*b*) D. Raatz, C. Innertsberger and O. Reiser, *Synlett*, 1999, 1907.
57 C. E. Song, C. R. Oh, E. J. Roh, S.-g. Lee and J. H. Choi, *Tetrahedron: Asymmetry*, 1999, **10**, 671.
58 K. R. Dress, L. J. Goossen, H. Liu, D. M. Jerina and K. B. Sharpless, *Tetrahedron Lett.*, 1998, **39**, 7669.
59 T. J. Donohoe, P. D. Johnson, M. Helliwell and M. Keenan, *Chem. Commun.*, 2001, 2078.
60 E. J. Corey and M. C. Noe, *J. Am. Chem. Soc.*, 1996, **118**, 11038.
61 R. Angelaud, O. Babot, T. Charvat and Y. Landais, *J. Org. Chem.*, 1999, **64**, 9613.
62 (*a*) L. Barboni, C. Lambertucci, G. Appendino, D. G. Vander Velde, R. H. Himes, E. Bombardelli, M. M. Wang and J. P. Snyder, *J. Med. Chem.*, 2001, **44**, 1576; (*b*) L. Barboni, C. Lambertucci, R. Ballini, G. Appendino and E. Bombardelli, *Tetrahedron Lett.*, 1998, **39**, 7177.
63 R. Angelaud, Y. Landais and K. Schenk, *Tetrahedron Lett.*, 1997, **38**, 1407.
64 P. Phukan and A. Sudalai, *Tetrahedron: Asymmetry*, 1998, **9**, 1001.
65 H. Han, J. Yoon and K. D. Janda, *J. Org. Chem.*, 1998, **63**, 2045.
66 R. M. Davey, Ph. D. Thesis, University of Sydney, 2002.
67 (*a*) S.-H. Lee, J. Yoon, S.-H. Chung and Y.-S. Lee, *Tetrahedron*, 2001, **57**, 2139; (*b*) S.-H. Lee, J. Yoon, K. Nakamura and Y.-S. Lee, *Org. Lett.*, 2000, **2**, 1243.
68 D. L. Boger, R. J. Lee, P.-Y. Bounaud and P. Meier, *J. Org. Chem.*, 2000, **65**, 6770.
69 D. L. Boger, R. M. Borzilleri, S. Nukui and R. T. Beresis, *J. Org. Chem.*, 1997, **62**, 4721.
70 (*a*) R. N. Atkinson, L. Moore, J. Tobin and S. B. King, *J. Org. Chem.*, 1999, **64**, 3467; (*b*) X. Li, R. N. Atkinson and S. B. King, *Tetrahedron*, 2001, **57**, 6557.
71 E. Medina, A. Moyano, M. A. Pericas and A. Riera, *Helv. Chim. Acta*, 2000, **83**, 972.
72 G. Li, R. Lenington, S. Willis and S. H. Kim, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1753.
73 C. Palomo, I. Ganboa, A. Kot and L. Dembkowski, *J. Org. Chem.*, 1998, **63**, 6398.
74 S. Crosignani, G. Desimoni, G. Faita and P. Righetti, *Tetrahedron*, 1998, **54**, 15721.
75 K. S. Kim, S. O. Choi, J. M. Park, Y. J. Lee and J. H. Kim, *Tetrahedron: Asymmetry*, 2001, **12**, 2649.
76 P. G. Andersson, D. Guijarro and D. Tanner, *J. Org. Chem.*, 1997, **62**, 7364.
77 R. M. Davey, M. A. Brimble and M. D. McLeod, *Tetrahedron Lett.*, 2000, **41**, 5141.
78 D. D. Hennings and R. M. Williams, *Synthesis*, 2000, 1310.
79 J.-C. Lee, G. T. Kim, Y. K. Shim and S. H. Kang, *Tetrahedron Lett.*, 2001, **42**, 4519.
80 S. J. Keding, N. A. Dales, S. Lim, D. Beaulieu and D. H. Rich, *Synth. Commun.*, 1998, **28**, 4463.
81 S. Chandrasekhar and S. Mohapatra, *Tetrahedron Lett.*, 1998, **39**, 6415.
82 S. Chandrasekhar, S. Mohapatra and J. S. Yadav, *Tetrahedron*, 1999, **55**, 4763.
83 B. Lohr, S. Orlich and H. Kunz, *Synlett*, 1999, 1139.
84 G. Cravotto, G. B. Giovenzana, R. Pagliarin, G. Palmisano and M. Sisti, *Tetrahedron: Asymmetry*, 1998, **9**, 745.
85 B. Cao, H. Park and M. M. Joullie, *J. Am. Chem. Soc.*, 2002, **124**, 520.
86 B. Herbert, I. H. Kim and K. L. Kirk, *J. Org. Chem.*, 2001, **66**, 4892.
87 M. H. Haukaas and G. A. O'Doherty, *Org. Lett.*, 2001, **3**, 3899.
88 C. E. Masse, A. J. Morgan, J. Adams and J. S. Panek, *Eur. J. Org. Chem.*, 2000, 2513.
89 J. S. Panek and C. E. Masse, *Angew. Chem., Int. Ed.*, 1999, **38**, 1093.
90 C. E. Masse, A. J. Morgan and J. S. Panek, *Org. Lett.*, 2000, **2**, 2571.
91 (*a*) E. Nandanan, P. Phukan, G. C. G. Pais and A. Sudalai, *Indian J. Chem., Sect. B*, 1999, **38**, 287; (*b*) A. Mandoli, D. Pini, A. Agostini and P. Salvadori, *Tetrahedron: Asymmetry*, 2000, **11**, 4039.
92 C. E. Song, J. W. Yang and H.-J. Ha, *Tetrahedron: Asymmetry*, 1997, **8**, 841.