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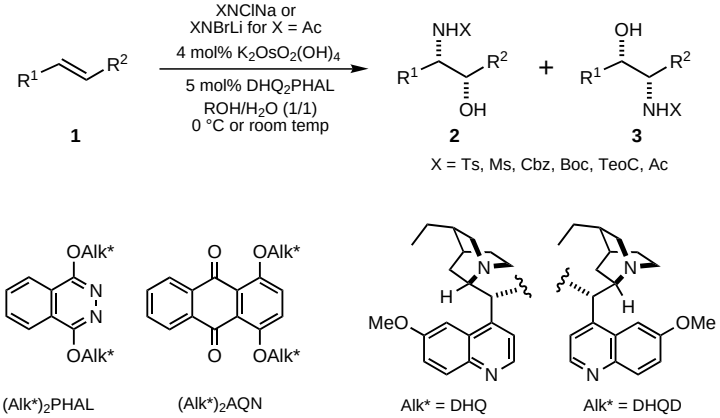
Sharpless Asymmetric Aminohydroxylation: Scope, Limitations, and Use in Synthesis

Peter O'Brien*

Since Sharpless' seminal contribution in 1996,[1] the catalytic and asymmetric conversion of alkenes into enantiomerically enriched N-protected amino alcohols [asymmetric aminohydroxylation (AA)] has rapidly become an extremely useful process. Using a reaction that is a close cousin of asymmetric dihydroxylation,[2] it is now possible to prepare amino alcohols (with different N-protecting groups) in good yields and high enantiomeric excesses from a range of alkene types. This is important since the β-amino alcohol functionality is found in many biologically active compounds and is therefore considered an important pharmacophore. Indeed, a large proportion of the recent papers on asymmetric aminohydroxylation have focussed on its application for the synthesis of biologically active compounds; these are summarized at the end of this article. The main purpose of this highlight is however to compare the yields, regioselectivities, and enantioselectivities obtained by using the different types of AA reactions. In addition, it is hoped that the present discussion will provide useful guidelines for those using Sharpless AA in synthesis.

Currently, there are six different methods available for carrying out asymmetric aminohydroxylations. All of the methods have originated from the Sharpless group and they differ only in the N-protecting group (*p*-toluenesulfonyl (Ts),[1] methanesulfonyl (Ms),[3] benzyloxycarbonyl (Cbz),[4] *tert*-butoxycarbonyl (Boc),[5, 6] 2-trimethylsilylethoxycarbonyl (TeoC),[7] or Ac[8]) that is introduced (Scheme 1). Each



Scheme 1. Overview of Sharpless asymmetric aminohydroxylation (AA).

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method uses a combination of osmium tetroxide (obtained from $K_2OsO_2(OH)_4$), alkaloid-derived ligands (e.g. 1,4-bis(dihydoquininyl)phthalazine ($(DHQ)_2PHAL$) or 1,4-bis(dihydoquininyl)anthraquinone ($(DHQ)_2AQN$)), and the Li or Na salt of an N-halogenated sulfonamide, alkyl carbamate, or amide in an alcohol/water solvent mixture; two regioisomers **2** and **3** can be produced from an unsymmetrical alkene such as **1**. As with asymmetric dihydroxylation, dihydroquinine (DHQ)- and dihydroquinidine(DHQD)-derived ligands produce enantiocomplementary results.

Table 1 contains a direct comparison of the reaction conditions of all six variants. They are very similar and only subtle differences between the conditions are noticeable.

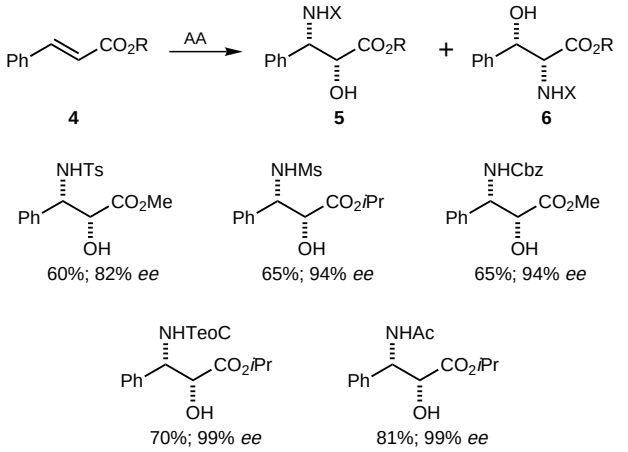
Table 1. Summary of the six different methods used for aminohydroxylation.

Method[a]	N Source (equiv)	Solvent	Temp [°C]	$(DHQ)_2PHAL$ [mol%]
A	TsNClNa (3.5)	*t*BuOH/water (1:1)[b]	RT	5
B	MsNClNa (3)	*n*PrOH/water (1:1)	RT	5
C	CbzNClNa (3)	*n*PrOH/water (1:1)[c]	RT	5
D	BocNClNa (3)	*n*PrOH/water (2:1)	0	6
E	TeoCNClNa (3)	*n*PrOH/water (1:1)	RT	5
F	AcNBrLi (1)	*n*PrOH/water (1:1.5)	4	5

[a] 4 mol% $K_2OsO_2(OH)_4$ used in each of methods A–F. [b] MeCN/water (1:1) also used as solvent. [c] *i*PrOH/water (1.5:1) and MeCN/water (1:1) also used as solvent.

Thus, for efficient introduction of a Boc-protecting group, the reaction is carried out at 0 °C in the presence of less water and more ligand (to minimize competing dihydroxylation).[5] With the sulfonamide and acetamide reactions (Methods A, B, and F), the *N*-haloamine salt is prepared from the corresponding *N*-haloamides, whereas for the carbamate reactions (Methods C, D, and E), the *N*-haloamine salt is prepared in situ from the carbamate and *tert*-butylhypochlorite/NaOH. As we shall see, the general trend is that higher yields and better enantioselectivities are obtained with sterically less demanding substituents [e.g. X = Ms (Method B), TeoC (Method E), or Ac (Method F)] on the nitrogen atom. In addition, the TeoC carbamate reaction has the highest rate of all of the processes and this means that lower catalyst loadings (e.g 2 mol% osmium) are possible. From a synthetic viewpoint, the Boc, Cbz, and TeoC protecting groups are the most readily removed.

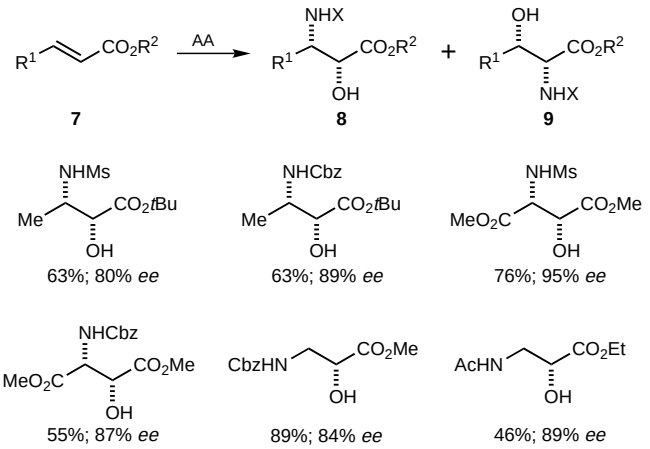
Cinnamates **4** have proved to be one of the most successful (and therefore popular) types of alkene substrates for AA reactions. Regioisomer **5** is produced preferentially when $(DHQ)_2PHAL$ is used, and a selection of results is presented in Scheme 2. The highest yields and enantiomeric excesses are obtained for the TeoC-carbamate (Method E) and the acetamide (Method F) processes; the higher yields probably reflect a better level of regioselectivity in these cases. It has recently been noted[9] that the preferred regioselectivity observed with $(DHQ)_2PHAL$ as a ligand can be overturned by changing to the related $(DHQ)_2AQN$ ligand (see Scheme 1 for ligand structure). Thus, Cbz-carbamate AA of methyl cinnamate **4** (R = Me) using $(DHQ)_2PHAL$ gave a 65% yield (ca. 7:1 regioselection) of pure regioisomer **5** (R = Me) of 94% *ee*, whereas the same reaction using $(DHQ)_2AQN$



Scheme 2. Asymmetric aminohydroxylation of cinnamates using $(DHQ)_2PHAL$.

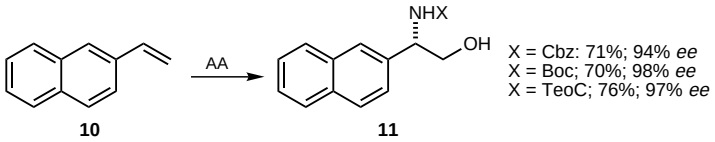
generated a 58% yield (ca. 4:1 regioselection) of pure regioisomer **6** (R = Me) of 95% *ee*. This is an amazing observation: the ligand affects the regioselectivity of the reaction but does not affect the *sense* and *degree* of asymmetric induction.

The results of aminohydroxylating some α,β-unsaturated compounds (similar in structure to the cinnamates) are presented in Scheme 3. From these results, it appears that Cbz-carbamate-based AA (Method C) is best for crotonates and acrylates, whereas the chloramine-M approach (Method B) is optimal for AA of *trans*-dimethylfumarate. The effect of ligand structure on the regioselectivity observed with crotonates and acrylates has not been reported to date.



Scheme 3. Asymmetric aminohydroxylation of crotonates, acrylates, and dimethylfumarate.

In contrast to α,β-unsaturated esters, styrenes and vinyl arenes were initially absent from the list of compounds which had been successfully aminohydroxylated. It was only with the advent of the carbamate- and acetamide-based processes that such compounds became viable substrates for AA reactions. A very detailed paper[5] has recently appeared on these transformations and a representative example is depicted in Scheme 4. AA of 2-vinylnaphthalene **10** using any of the

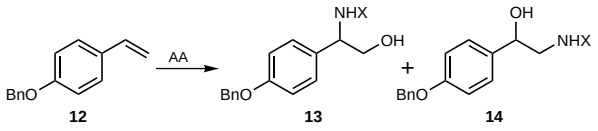


Scheme 4. Asymmetric aminohydroxylation of 2-vinylnaphthalene.

carbamate-based processes generated amino alcohol **11** of $\geq 94\%$ *ee* in $\geq 70\%$ yield.[5, 10] The reaction tolerates equally well electron-donating and -withdrawing substutuents on the aromatic ring in substituted styrenes. However, these results do hide to some extent the fact that *careful* column chromatography is generally required to separate the major product from around 15% of the regioisomeric amino alcohol and from the excess carbamate.

The regioselectivity observed in AA reactions of styrenes is found to be dependent on the nature of the ligand, the solvent, and the N-protecting group introduced (Table 2).[5, 8] Thus, in

Table 2. Aminohydroxylation of stryenes—dependence of regioselectivity on ligand type and solvent.

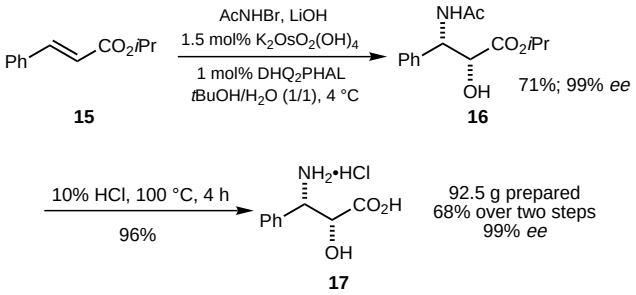


X	Conditions	**13**:**14**
Ac	$(DHQD)_2PHAL$ (*n*PrOH/water)	2.5:1[a]
Ac	$(DHQD)_2PHAL$ (MeCN/water)	1:2.4[a]
Ac	$(DHQD)_2AQN$ (MeCN/water)	1:9[a]
Cbz	$(DHQ)_2PHAL$ (*n*PrOH/water)	7.3:1
Cbz	$(DHQ)_2PHAL$ (MeCN/water)	3:1
Cbz	$(DHQ)_2AQN$ (MeCN/water)	1:3

[a] Not separable by chromatography.

the AA of styrene **12**, amino alcohols **13** are the major products using $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$ in an alcohol/water solvent mixture but increasing amounts of amino alcohols **14** are produced when the solvent is changed to acetonitrile/water and the ligand is changed to $(DHQ)_2AQN$ or $(DHQD)_2AQN$. The remarkable ligand-dependence is very similar to that observed with AA reactions of cinnamates (vide infra) but none of these regioselectivity issues are easily explained. Interestingly, the enantiomeric excesses of amino alcohols **13** and **14** are similar and high with the acetamide-based process (F), whereas with the Cbz-carbamate process (C), amino alcohol **13** is obtained with considerably higher enantiomeric excess than its regioisomer **14**. Unfortunately, although better regioselectivity (and higher enantioselectivity) was obtained for amino alcohol **14** over **13** using the acetamide-based AA process, the two products were inseparable by chromatography. A recent report[6] on AA reactions of other styrenes has revealed the surprising fact that the regioselectivity observed with $(DHQ)_2PHAL$ is different to that obtained with $(DHQD)_2PHAL$ even though the enantiomeric excesses of the products (opposite absolute configuration) were essentially the same. In these examples, lower levels of regioselectivity manifest themselves in lower isolated yields. Clearly, the nature of the ligand ($(DHQ)_2$-PHAL versus $(DHQD)_2PHAL$ versus $(DHQ)_2AQN$) can have a dramatic and unexpected effect on the regioselectivity of the AA reactions of styrenes (and almost certainly other alkenes, but the results have not been published).

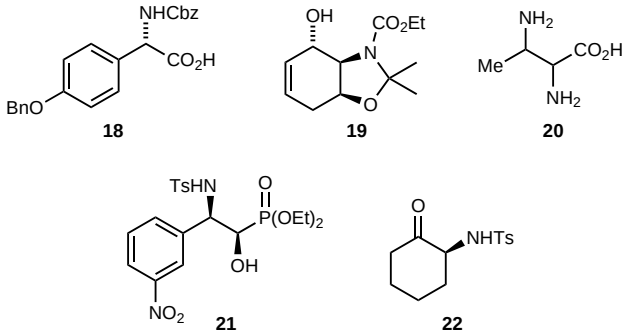
The previously described developments of the AA reaction have meant that its application to synthesis has now become appropriate. A useful example is Sharpless' efficient, large-scale, concise, and eminently attractive preparation of the precursor to the Taxol side chain **17** (Scheme 5).[8] Thus, an



Scheme 5. Large-scale two-step synthesis of precursor to the Taxol side chain.

AA reaction on isopropyl cinnamate (120 g) that employed just 1.5 mol% $K_2OsO_2(OH)_4$ (3.5 g) and *N*-bromoacetamide generated amino alcohol **16** of 99% *ee* in 71% yield after recrystallization. This was readily hydrolyzed to give enantiomerically pure hydrochloride salt **17** (92.5 g; 68% yield over the two steps).

A number of other significant results in the use of AA in synthesis have now appeared. For example: aminohydroxylation of styrenes has been used in a two-step synthesis of N-protected amino acids such as **18**;[5] a diastereo- and enantioselective aminohydroxylation reaction of a dienylsilane was used to prepare enantiomerically pure allylic alcohol **19** (Scheme 6);[11] all four isomers of 2,3-diaminobutanoic acid



Scheme 6. Examples of use of asymmetric aminohydroxylation in synthesis.

20 have been prepared by using carbamate-based AA of *tert*-butyl crotonate as the pivotal point in the synthetic approach;[12] chloramine-T-based AA reactions on vinyl phosphonates[13] and silyl enol ethers[14] have been used to synthesize enantiomerically enriched sulfonamides **21** and **22** respectively. More recent synthetic developments include

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the direct introduction of heterocycles in AA reactions,[15,16] the application of AA methodology in the preparation of a fragment for the total synthesis of the vancomycin aglycon,[17] and a silica-gel-supported variant of AA.[18] All of these examples, some of which have been carried out on a reasonably large scale, serve to illustrate that AA has a promising synthetic future. A few issues, such as lack of regioselecitivity and poor substrate scope in certain cases, need to be resolved but it is instructive to see what impressive achievements have been reached in such a short space of time. With six different methods currently at our disposal, we are surely not too far from being able to convert any alkene into an amino alcohol in a catalytic and asymmetric fashion.

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Keywords: amino alcohols · aminohydroxylations · asymmetric catalysis · asymmetric synthesis · osmium

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