The Sharpless Asymmetric Aminohydroxylation – Scope and Limitation

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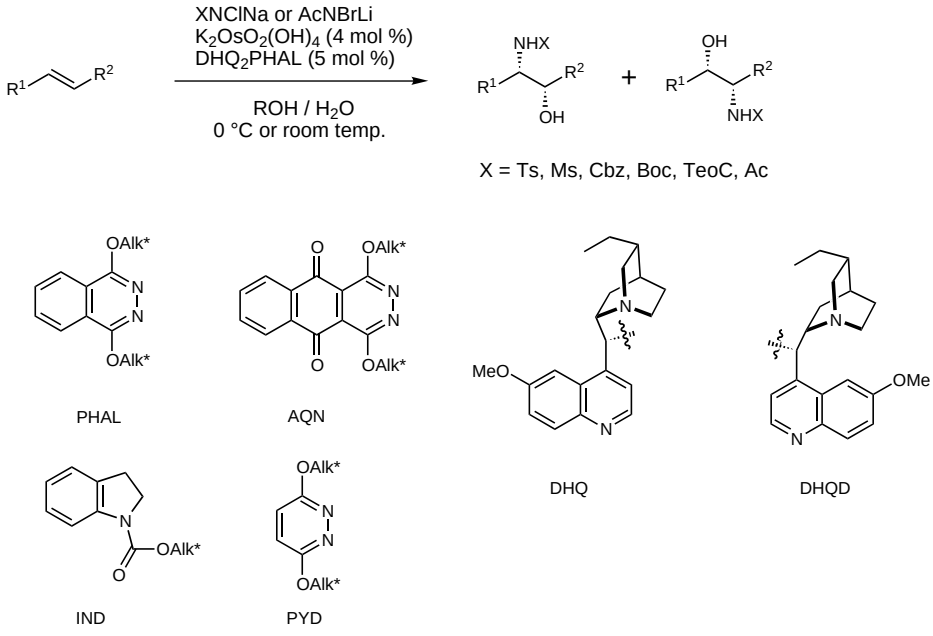
Abstract: The asymmetric aminohydroxylation (AA) has emerged as a valuable tool in organic synthesis. Recent developments, such as ligandless variants, new nitrogen reagents and new substrates have considerably broadened the utility of the process. Nevertheless, the understanding of the AA, both in terms of mechanism as well as applicability to common synthetic tasks is still limited. This article summarizes the scope and limitation of the AA with special emphasis on recent advances.

Keywords: amino alcohol; aminohydroxylation; asymmetric catalysis; dihydroxylation; osmium

1 Introduction

The asymmetric aminohydroxylation (AA), although only discovered[1] by Sharpless et al. in 1996, has rapidly become an invaluable synthetic tool in organic chemistry. Its great value is given in the possibility of enantioselectively introducing a 1,2-amino alcohol functionality, which is most important for the construction of biologically active compounds and chiral ligands, from readily available alkenes (Scheme 1). Initially, only an *N*-tosyl protected amino group could be transferred, but quite rapidly other nitrogen sources transferring the amino group with standard protecting groups such as BOC[2] (*tert*-butoxycarbonyl) or Cbz[3] (benzyloxycarbonyl) were discovered, broadening greatly the utility of the AA. Moreover, by appropriate choice of the ligands, the regioselectivity of the reaction can be controlled quite efficiently.[4] There have been



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

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already a number of reviews[5] about the AA. In contrast to these, this article puts forth an analysis of the scope and limitation of the AA based on the mechanistic proposals discussed in the literature, rather than giving a complete overview on recent applications.

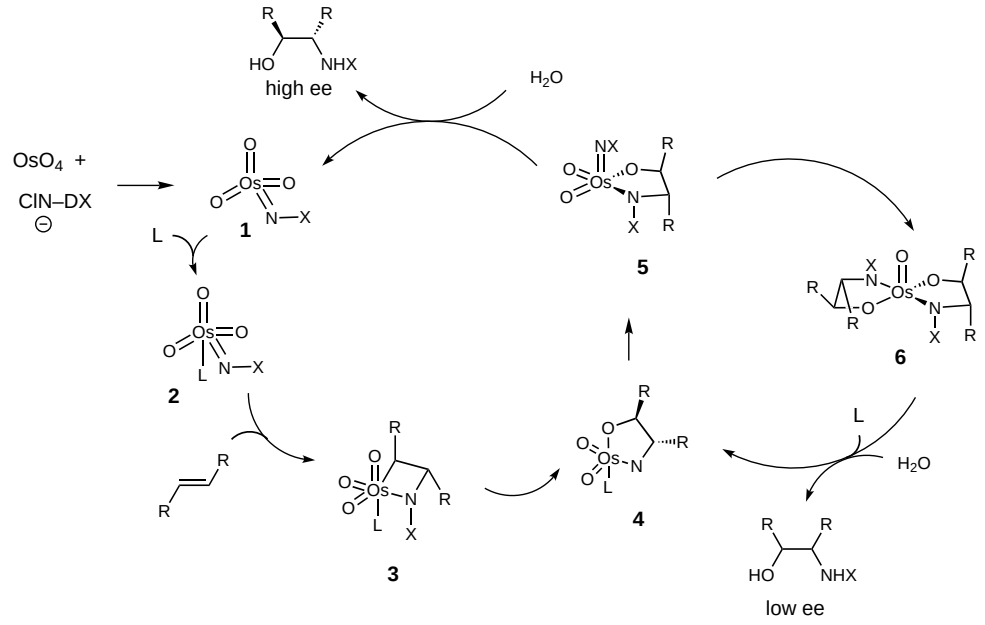
2 Mechanism and Consequences for Alkenes in the AA

Because of the distinct similarities of the AA to the asymmetric dihydroxylation (AD), the mechanism discussed for the AA resembles in many aspects that of the AD (Scheme 2).

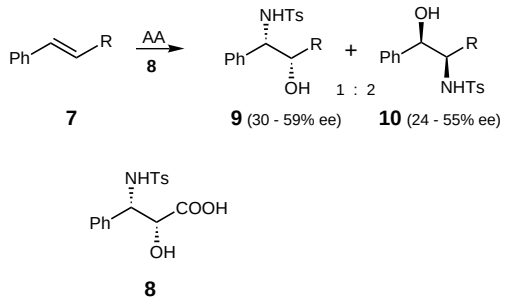
The reaction is initiated with the formation of imidotrioxoosmium(VIII) **1** from osmium tetroxide and an appropriate nitrogen source. Coordination of a chiral ligand L leads to the active complex **2**, which is ready to react with the alkene. Sharpless suggests in analogy to the AD the formation of the osmaazetidine **3**, which subsequently undergoes rearrangement to the adduct **4**. This proposal nicely explains that the nitrogen is normally introduced at the β-position to an electron-withdrawing group in the alkene, simultaneously coordinating the electrophilic osmium center at the α-position. However, the reversal of regioselectivity in the AA[6] by the use of the AQN instead of the PHAL ligands – although the mechanistic reasons for this are not understood at all – sheds doubt on this explanation. Obviously, the substrate orientation within the binding pocket of the AQN ligands is reversed with respect to the PHAL ligands, suggesting that stereoelelctronic factors in the control of the regioselectivity are less dominant. Moreover, in light of mechanistic proposals for the AD refuting the [2 + 2] pathway,[7] the direct formation of **4** by a [3 + 2] cycloaddition might be also feasible for the AA. Displacement of the chiral ligand L by another nitrogen reagent results in **5**, which has two-fold significance in the catalytic cycle. Hydrolysis, which is promoted by solvent mixtures containing 50% of water, releases the amino alcohol and regenerates **1**. In addition, from **5** a second catalytic cycle might also be initiated by reaction with another alkene to give rise to **6**. Since amino alcohols have been proved to be successful ligands in a variety of catalytic processes, this pathway poses the intriguing question if the AA might be developed as an autocatalytic process.

Indeed, it was recently discovered that products obtained by the aminohydroxylation itself can serve as ligands.[8] Thus, the AA of styrene (**7**) proceeds in high yields to the regioisomeric amino alcohols **9** and **10** in the presence of catalytic amounts of **8**, being the AA product of cinnamic acid, with moderate, but nevertheless significant enantioselectivity (Scheme 3).

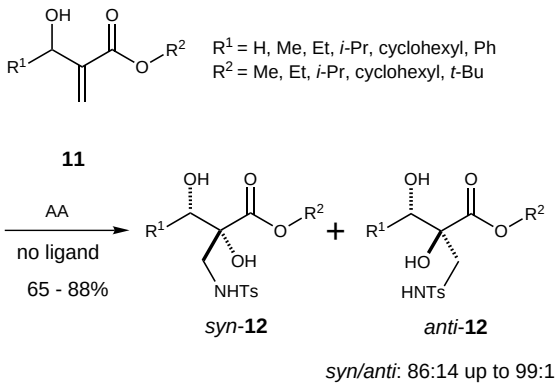
Related to the previous example is the report that the AA of carboxylic acids,[9] carboxylic amides,[10] pinenes or camphenes,[11] proceeds well in the absence of *any ligand*. Likewise, Baylis–Hilmann adducts **11** are also privileged starting materials, giving *syn*-**12** with good preference over the diastereomer *anti*-**12** without the need of promotion by ligands (Scheme 4).[12] The amino group is exclusively introduced at the terminal end of the alkene, however, it is interesting to note that addition of the ligands of the AA does not seem to influence the course of the reaction at all: in the presence of $(DHQ)_2PHAL$ the products were obtained racemically, i.e., no kinetic resolution seems to have taken



Scheme 2. The two possible catalytic cycles in the AA.



Scheme 3. AA adducts of cinnamic acid serve as ligands for the AA.



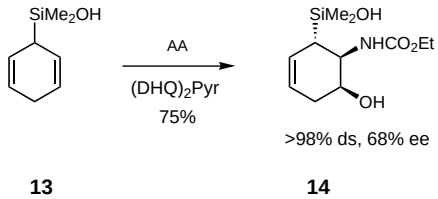
Scheme 4. Asymmetric aminohydroxylation of Baylis–Hilmann adducts.

place, with the hydroxy group in **11** obviously acting as a heteroatom directing group.[13]

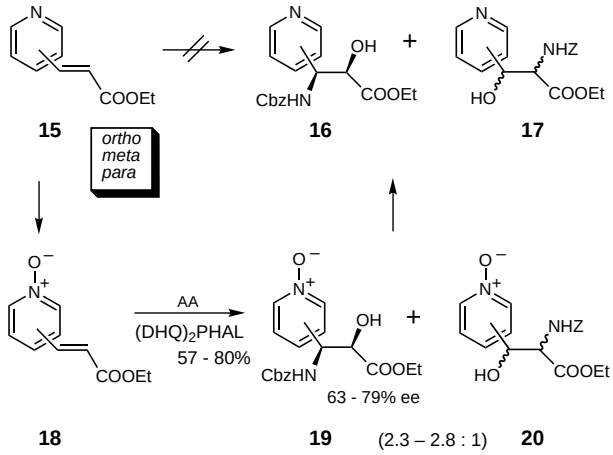
In contrast to the attempt of realizing a kinetic resolution described above, a quite remarkable desymmetrization of the *meso*-1,4-diene **13** was achieved using the AA in the presence of the $(DHQ)_2Pyr$ ligand: **14** was obtained with complete regioselectivity, indicating a strong directing effect of the silyl group due to its β-effect (Scheme 5).[14]

Heteroaromatic alkenes have been found to be especially useful substrates for the AA, since the products offer a considerable potential for further synthetic transformations.[15]

While acrylates substituted with a furan, thiophene, or indole moiety serve as excellent substrates in the AA,[16] pyrroles and pyridines fail to give the title reaction.[16a]



Scheme 5. Desymmetrization of cyclohexa-1,4-dienes *via* the AA.



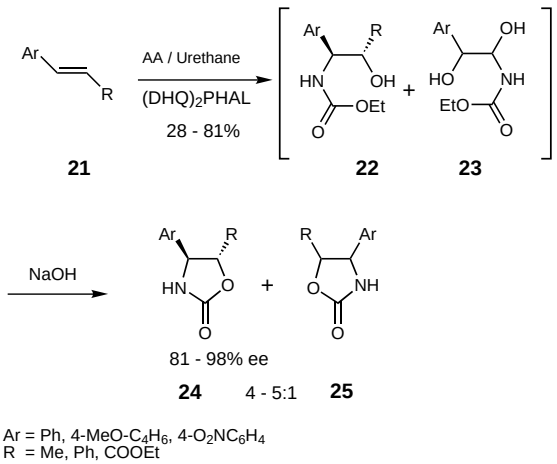
Scheme 6. Indirect AA of pyridinyl acrylates *via* the corresponding *N*-oxides.

Steric hindrance exhibited by the *N*-protecting group in pyrroles might prevent the AA in these substrates, but the failure of pyridine acrylates **15** seems to be a result of interference with the pyridine nitrogen (Scheme 6). Indeed, the AA of styrene under normal conditions is inhibited when pyridine is added as an external coligand. However, the corresponding acrylates **18** of pyridine *N*-oxides can be used alternatively in the AA and subsequently reduced, thus providing an indirect solution to access aminohydroxylated products of pyridine-substituted acrylates.[16a] It was interesting to note that the major regioisomer **19** was formed with modest levels enantioselectivity, while the minor isomer **20** was obtained in racemic form. This approach was used for the synthesis of the pyridyl analogue of the side chain of taxol, which had been demonstrated to yield a considerable more potent taxol derivative than the natural product itself.[17]

3 New Nitrogen Sources

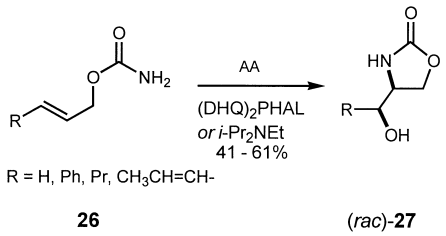
During the last three years a number of new nitrogen sources, such as *tert*-butylsulfonamide,[18] primary amides[19] and carbamic acid ethyl ester,[20] were introduced, further demonstrating that a broad variety of imido ligands can be transferred in the catalytic cycle of the AA. Urethanes can be utilized as well, giving rise to oxazolidin-2-ones **24** and **25**, which are in general of interest as chiral auxiliaries, in a one-pot procedure (Scheme 7).[21]

Similarly, an intramolecular variant utilizing carbamates **26** derived from allylic alcohols has been developed using an amine like Hünig's base as additive (Scheme 8).[22] The products were obtained with complete regio- and diastereocontrol, but surprisingly, only in racemic form when chiral ligands like $(DHQ)_2PHAL$, being established for the AA, were employed.



21 22 23 24 25

Scheme 7. Oxazolidones *via* the AA using urethanes as the nitrogen source.



26 (*rac*)-27

Scheme 8. An intramolecular variant of the AA.

4 New Ligands and Catalysts

Based on the established alkaloid PHAL ligands, a number of modifications have been reported which have led to alternative ligands, mainly influencing the regioselectivity of the AA (*cf.* Scheme 1).[23] In that context, the PHAL ligand **28** immobilized to an organic copolymer has been successfully prepared (Figure 1), demonstrating the AA with a heterogeneous catalyst.[24] Selectivities up to 87% were achieved in the AA of isopropyl *trans*-cinnamate, compared to 96% ee with the corresponding non immobilized ligand.

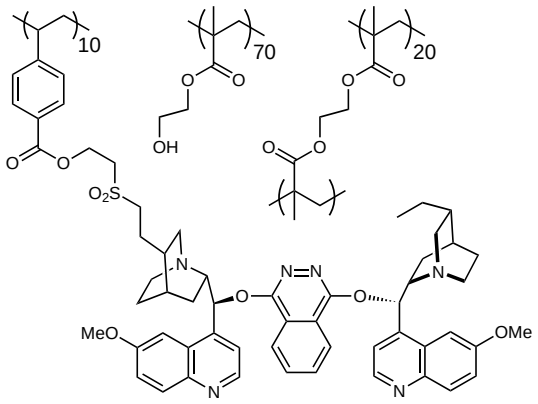


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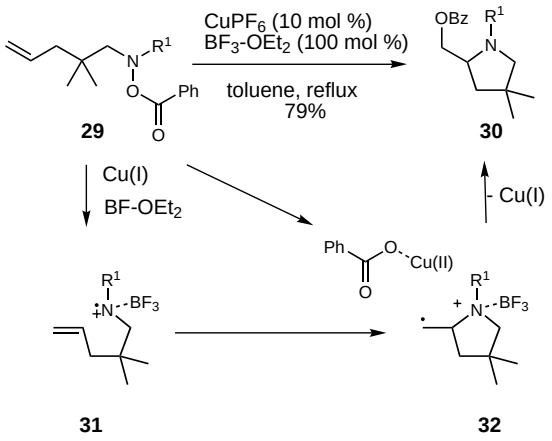
Figure 1. A polymer-bound ligand for the AA.



29 30 31 32

Scheme 9. Cu(I) catalyzed aminohydroxylation of hydroxylamines.

While osmium is the metal of choice for the AA, there has been a recent report of the copper(I)-catalyzed intramolecular aminohydroxylation in the presence of BF_3-etherate starting from hydroxylamines (Scheme 9).[25] The mechanism of this reaction is distinctively different, involving radicals as intermediates.

5 Conclusion

There remain still quite a few conceptual advances to be discovered in the asymmetric aminohydroxylation, broadening further the scope and limitations of this process. On the other hand, the utility of the AA is demonstrated in many applications now, giving ample proof that this reaction has become an indispensable tool in organic synthesis.

Acknowledgements

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