ORGANIC LETTERS

2000
Vol. 2, No. 17
2667−2669

Concentration Dependence of the Sharpless Asymmetric Amidohydroxylation of Isopropyl Cinnamate

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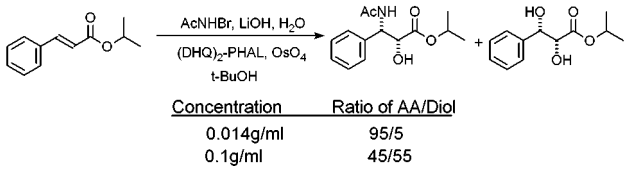
Received June 13, 2000

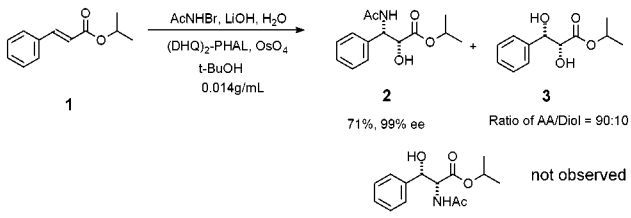
ABSTRACT



A need to prepare large quantities of phenylisoserine for the semisynthesis of paclitaxel prompted us to examine the Sharpless amidohydroxylation reaction to see if it could be run at concentrations greater than those reported in the literature. During these investigations, we discovered that the amount of amidoalcohol produced in the reaction decreased while the diol side product increased as the concentration increased. We discovered that acetamide suppresses this side reaction and allows us to run the chemistry at 0.1 g/mL rather than the 0.014 g/mL reported in the literature.

The osmium-promoted aminohydroxylation reaction was first discovered in the early 1970's by Sharpless[1] and further developed by him over the next 25 years into a truly useful reaction. In its current form the reaction is catalytic in osmium and produces amidoalcohols with excellent enantioselectivities. The most recent iteration of the process makes use of the commercially available *N*-bromoacetamide as both the reoxidant for osmium and as the nitrogen source as illustrated in Scheme 1.[2] Regioselectivity is excellent, especially in olefins with well-differentiated substituents. Our work on the development of a semisynthesis of paclitaxel[3] led us to use this chemistry for the preparation of the required phenylisoserine side chain. Initially we carried out two large scale runs to produce about 200 g of material, but it became clear that scale-up of this reaction would be problematic because of the very low volume efficiency (0.014 g/mL) used to run the reaction. Since most reactions can typically be run at concentrations much higher than the procedures reported in the literature, we simply ran the process at a higher concentration. Unfortunately, the normal result was not obtained; instead, a large amount of the unwanted diol **3** was obtained. This is graphically illustrated in Figure 1 over the concentration range of 0.10−0.017 g/mL. At higher

Scheme 1. Sharpless Amidohydroxylation



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(2) Bruncko, M.; Schlingloff, G.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1483.
(3) For a review on the semisynthesis of paclitaxel, see: Wuts, P. G. M. *Current Opin. Drug Discovery Dev.* **1998**, *1*, 329.

10.1021/ol006198+ CCC: $19.00
Published on Web 07/25/2000

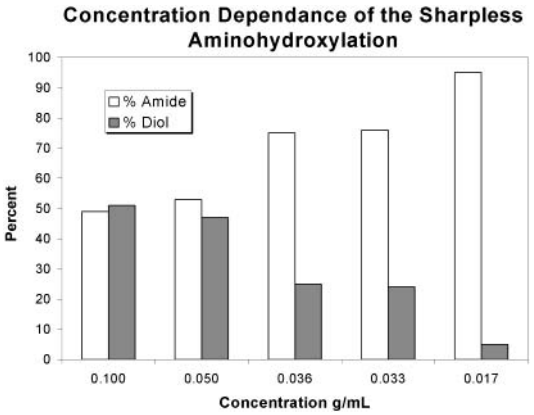

Figure 1. Amidoalcohol/diol ratio vs concentration.

concentrations, there was some variation in the AA/diol ratio, which we attribute to inhomogeneity of the reaction mixture.

In an attempt to elucidate an explanation for these results, we considered the possible catalytic cycles involved. Figure 2 presents a number of possible pathways that may contribute

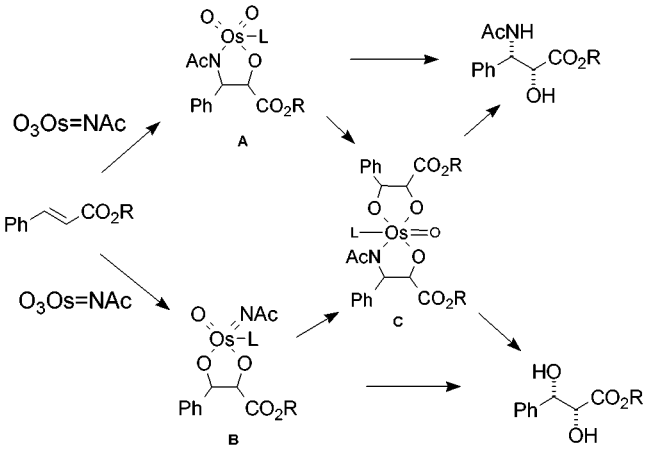

Figure 2. Intermediates in the amidohydroxylation reaction.

to the formation of the diol. In the desired transformation, intermediate **A** is hydrolyzed to the amidoalcohol. If the developments observed by Sharpless in the dihydroxylation can be extended to the amidohydroxylation reaction, the intermediate **C** can be invoked as a source for the diol. In this case hydrolysis of **A** must be sufficiently slow that oxidation and a second addition of cinnamate occur in competition with hydrolysis.[4] In the dihydroxylation, the addition of a second alkene causes a loss of enantioselectivity because enantioselectivity for the second addition is small and often in the opposite direction as the first. In this case, we do not observe a loss of enantioselectivity in the diol. In fact, we typically observe ee's in the 80−90% range for the diol isolated from these reactions. It is possible that **B** plays a role in the formation of the diol. Rubenstein and Svendsen[5] have shown that in a stoichiometric aminohydroxylation with *t*-BuN═OsO_3 considerable diol can be formed. The relative amounts were also ligand dependent.

Because it was known that OsO_4 reacts with *t*-$BuNH_2$ to form *t*-BuN═OsO_3,[6] we thought that addition of excess acetamide to the reaction would improve the AA/diol ratio in the event that the diol was formed by direct reaction with OsO_4. *Suprisingly, an improvement was observed, but not for the anticipated reason*. When the reaction was performed at 0.05 g/mL with 1 equiv of $AcNH_2$,[7] the amidoalcohol (AA) is formed in 60% yield and 99% ee after isolation and crystallization. The AA/diol ratio is typically 95/5 under these conditions. OsO_4 does not react with acetamide directly to give O_3Os═NAc, and thus the improvement occurs by an as yet unknown mechanism. Not until the mechanistic details for the formation of O_3Os═NAc are elucidated will it be possible to sort out why acetamide has the observed beneficial effect of reducing the level of diol formation. We did attempt to prepare O_3Os═NAc in an NMR tube by mixing OsO_4 and $AcNH_2$ and then adding the cinnamate, but no amidoalcohol was formed, indicating that the key intermediate was not formed. Of some interest is the fact that addition of either trifluoroacetamide or urea completely shuts down the reaction—no diol or amidoalcohol is formed. Methanesulfonamide is known to improve the dihydroxylation reaction because it increases the rate of hydrolysis of the osmate ester.[8] In the AA reaction, $MsNH_2$ has no beneficial effect and large quantities (70%) of the diol are still formed. On the other hand, when propionamide is added to the reaction in place of acetamide, both the propionyl and acetyl derivatives are isolated. When the experiment is carried out in reverse with *N*-bromopropionamide[9] and acetamide, a similar result is obtained. However, when *N*-bromoacetamide is replaced with *N*-bromopivalamide, no reaction occurred. We anticipated that the crossover may be a result of bromide exchange, but the experiment with *N*-bromopivalamide cast serious doubt on this scenario. Simple amide exchange by some type of addition−elimination mechanism is probably occurring that is competitive with the amidohydroxylation reaction.

During the development work we have found that some benzaldehyde along with some brominated byproducts, which could not be purified sufficiently for characterization, were produced during the oxidation. These would account for some of the material losses observed. It is known that alkene cleavage is a possible side reaction in oxidations with OsO_4.[10,11]

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(7) Lesser amounts of acetamide gave inconsistent results.

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Overall, we have discovered a very interesting concentration dependence on the Sharpless AA reaction. Moreover, we have developed conditions that will allow us to run the reaction with much greater volume efficiency than that in the original literature report by simply including a stoichiometric amount of $AcNH_2$. Much work remains to be carried out before this reaction is really understood.

Acknowledgment. We thank Eric Seest of the Physical and Analytical Group for help with the determination of enantiomeric excesses.

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(11) **Experimental Procedure.** Lithium hydroxide (2.4 g) and osmium tetroxide (0.61 g) are dissolved in water (20 mL) and stirred for 5 min. $(DHQ)_2PHAL$ (2.05 g) is dissolved in t-BuOH (80 mL) and added to the mixture. The mixture is stirred for 15 min. Acetamide (3.11 g) is dissolved in water (110 mL) and added to the mixture. The mixture is cooled to 0−5 °C. Isopropyl cinnamate (10 g)followed by *N*-bromoacetamide (8.05 g) is added to the flask. The reaction mixture is stirred at 0−5 °C until reaction is complete as determined by HPLC. The reaction is quenched with aqueous sodium sulfite (6 g in 100 mL water) and warmed to 15−25 °C. The reaction is extracted with CH_2Cl_2. The combined organic layers are stirred with magnesol (20 g) for 30 min and filtered. The organic is distilled to dryness. Methyl *tert*-butyl ether (20 mL) is added, and the mixture is stirred until a slurry forms. Hexane (20 mL) is added to complete precipitation. The slurry is filtered, washed with 50/50 MTBE/hexane, and dried with nitrogen. (60% yield (8.3 g) >97% ee).