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Process Development of the Sharpless Catalytic Asymmetric Dihydroxylation Reaction To Prepare Methyl (2*R*,3*S*)-2,3-Dihydroxy-3-phenylpropionate

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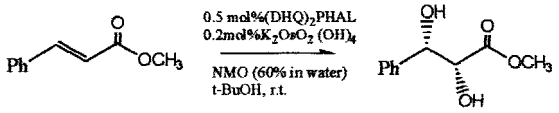
Abstract:

A typical Sharpless catalytic asymmetric dihydroxylation (ADH) process to make methyl (2*R*,3*S*)-2,3-dihydroxy-3 phenylpropionate has been successfully developed. The ADH reaction was exothermic and complete in 2−3 h without affecting the optical purity and yield. The major impurity of methyl (2*R*)-hydroxy-3-keto-phenylpropionate, which may seriously damage the quality of diol, has been identified and removed properly in the process.

The Sharpless catalytic asymmetric dihydroxylation (ADH) of olefins with osmium tetroxide in the presence of cinchona alkaloid derivatives has been widely used in chiral drug intermediate and natural product syntheses.[1] The ADH reaction is one of the most reliable and practical methods in Taxol side chain synthesis.[2a−d] However, there were limitations to performing the ADH reaction on a large scale. In recent years, many reports[3] appeared, exploring the possibility of repetitive use of osmium tetroxide to reduce the cost and toxicity. There were also reports about the development of polymer-bound cinchona alkaloid derivatives in heterogeneous ADHs, which were, as reported, still suffering from many drawbacks such as low reactivity, poor enantioselectivity, long reaction times, and poor yield.[3] Our earlier experiments on the ADH of the *trans*-methyl cinnamate−vicinal diol process ran into many important issues, one of which was about the previously unnoted exothermic effect and its impact; the other major issue was about the impurity profile and osmium removal.



As reported in the enantioselective synthesis of the Taxol C-13 side chain through asymmetric dihydroxylation, most of the reactions were carried out at room temperature (25 °C), with no particular report about the exothermic effect. The standard ADH temperature was at 0 °C;[4] however, one literature paper reported that the temperature actually had no remarkable effect on ee % in a range from −100 to 78 °C in some specific ADH reactions.[5]

Here we report our solutions for successful, efficient, industrial process development of the diol intermediate for the taxol side chain synthesis. Commercial methyl cinnamate was subjected to the *N*-methylmorpholine *N*-oxide (NMO)-based ADH process at room temperature. The ligand, 1,4-bis (9-*O*-dihydroquinine) phthalazine [$(DHQ)_2PHAL$] used in only 0.5 mol % NMO, was used as the cooxidant instead of $K_3[Fe(CN)_6]-K_2CO_3$, which was found impractical on a large scale.[6] The reaction was run in *t*-BuOH/water. We found that the reaction was complete in 2−3 h rather than 20 h with an obvious exothermic phenomenon not reported in the original.[7] Without control of the temperature, the exothermic process would drive the temperature as high as 35−40 °C. Control of the reaction temperature at 25 °C would drag the reaction time to about 20 h. In terms of the enantioselectivity, the 2−3 h reaction at 35−40 °C would not compromise the optical purity and yield in comparison with the 20 h reaction at 25 °C; in both cases, the ee % remained the same in the range of 87−90%. There had always been a problem of impurity removal following the literature work-up process, and the result of this process[7] was inconsistent in impurity level. Later on, we identified two impurities, one of which was the over-oxidized product as the β-keto material, and the other, NMO. It was assumed that the β-keto material resulted from over-oxidation of the transitional diol intermediate complex, which could be characterized from the HPLC monitoring (see Figure 1). The unnecessary, over-long, agitation time of the oxidation tremendously increased the impurity level. The addition of Na_2SO_3 actually played an important role in removing this complex by reduction of the osmium(VIII) to osmium(VI) which was more highly soluble in the aqueous phase. We found that the 2−3 h agitation of aqueous Na_2SO_3 reported in the original literature[7] was not long enough to remove the transitional intermediate complex (by HPLC).

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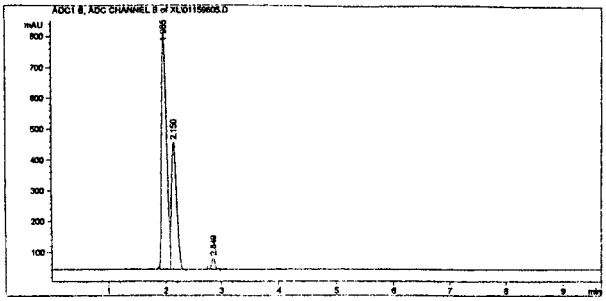
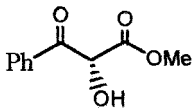


Figure 1. **β-Keto impurity profile by HPLC after 2-h reaction time.**

Table 1. **Variation of *T* °C/time Impact of Na_2SO_3**

	ADH rxn		Na_2SO_3 workup		ee		
entry	°C	time	°C	time	crude	final	yield %
1	25	21	25	3	87	99.8	59
2	25	21	23	18	88	99.7	65
3	35	3	25	18	87	99.8	73
4	35	3	45	0.5	87	99.8	76

The β-keto material was identified has the following structure:



From the in-process data of HPLC, the start material was identified at 2.849 min and started shrinking very fast once the reactants mixed, and meanwhile the product diol of 1.985 min peak grew until all the start material disappeared. A companion half-height peak at 2.150 min behind the product was also present with the diol. We assumed that to be the transitional complex of the osmium(VIII) with the resulting diol. Efficient removal of this 2.150-minute peak by proper treatment with aqueous Na_2SO_3 was very helpful in the diol quality control, and there was a direct relationship between the impurity level and the 2.150-minute peak existence. With all of the 2.150-minute peak removed, the diol would be very good in quality; otherwise, the diol with a lot of the β-keto impurity. On the basis of the observation, we designed a new work-up process by stretching the agitation time of Na_2SO_3 from 2 h to 18 h for which the 2.150-min. peak would eventually disappear, shown by HPLC. Later on, we changed the agitation of 18 h at 25 °C to a 35 min at 45 °C, monitoring by HPLC. With this change we found that the diol quality and yield were tremendously improved see Table 1).

Entries 3 and 4 products obtained are snow-white needle-like crystals, while those of entries 1 and 2 from the old process were off-white, poor looking solids. This process proved very successful in the pilot production of 50-kg scale, during which the exothermic effect was controllable and no thermal runaway was observed (in any case, the reaction temperature should be closely controlled under 40 °C). The newly developed process was very reliable and consistent in the pilot production and manufacturing.

Experimental Section

Preparation of methyl (2*R*,3*S*)-2,3-dihydroxy-3-phenyl-propionate. In a 1000 L reactor were charged 50 kg (308.3 mol, 1×) of methyl cinnamate and 155 L (3.1×) of *t*-BuOH, then 1.2 kg (1.54mol, 0.024×) of $(DHQ)_2PHAL$, 235 g (0.638 mol, 4.7×) of K_2OsO_4, and 93 L (1.86×) of NMO (50%). The reaction mixture was agitated at room temperature (23 °C); after 2 h, the exothermic effect drove the temperature maximum up to 40 °C (the temperature should be controlled under 40 °C). In-process HPLC monitoring after 2 h of reaction showed the reaction complete. After the temperature came back to rt, 46.3 kg (367 mol, 0.926×) of sodium sulfite dissolved in 155 L water were charged in, and the temperature was kept at 45 °C for 30 min. At the end of agitation, the reaction was monitored by HPLC, and when the Os−cinnamate complex peak was <2%, the agitation was stopped, and the mixture was allowed to stand for 15 min.. After the phase cut, the *t*-BuOH phase was concentrated into half the volume (about 360 L) by vacuum distillation and extracted three times with the ethyl acetate. The combined organic phase 770 L was washed with 10% NaC1 90 L twice. The aqueous phase was extracted with ethyl acetate twice. The combined organic phase was concentrated to make sure all of the ethyl acetate was stripped out of the system by adding toluene during the distillation (determined by GLC). The total volume of the organic phase was kept at about 185 L (3.7×) at the end of the distillation, and then 10 L of heptane was added. The temperature was lowered to about 5−10 °C, and the crystals were formed and agitated for another hour and then filtered, and vacuum-dried at 40 °C; the crystals weighed about 41.9 kg. (Yield: 70%, ee > 98%. Chemical purity: 99.9%, mp 85−86 °C.) The ee % was determined by GLC on β-cyclodextrin, J&W CDX-B column, 165 °C; $[\alpha]_D$ + 3.4° (*c* 1.19, EtOH); ^{1}H NMR ($CDCl_3$ 400 MHz) δ_H 2.89 (br, 1H), 3.21 (s,3H), 4.36 (d, J = 2.8 Hz, 1H), 5.01 (d, J = 2.8 Hz,1H), 7.36 (m,5H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ_C 173.1, 139.9, 128.4, 128.1, 126.2, 74.7, 74.4, 52.8.

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