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Asymmetric dihydroxylation of *trans*-cinnamates under high-pressure conditions: substantial increase of turnover number

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Abstract—Under high-pressure conditions, a substantial increase in the turnover number was observed in the osmium-catalyzed asymmetric dihydroxylation of *trans*-cinnamate derivatives. © 2001 Elsevier Science Ltd. All rights reserved.

The osmium-catalyzed asymmetric dihydroxylation (AD) of alkenes using cinchona alkaloid derivatives as chiral ligands is one of the most popular synthetic methods that has been devised and continuously improved by Sharpless et al.¹ In particular, the catalytic systems based on bis-cinchona alkaloids, 1,4-bis(9-O-dihydroguininyl)phthalazine such as ((DHQ)₂PHAL) and 1,4-bis(9-O-dihydroquinidinyl)phthalazine ((DHQD)₂PHAL), have received a great deal of interest, due to their broad scope of substrates, high enantioselectivities² and substantial rate-acceleration effect.3 Enzyme-like non-covalent binding in a binding pocket of this type of ligands seems to be the cause of the substantial rate accelerations and the ability to deliver high enantioselectivities.^{3b,4} However, the relatively low turnover numbers of this quite expensive catalytic system has limited large-scale applications. Very recently, Reiser et al. have reported that the volume of activation for the osmium-catalyzed non-AD of ethyl trans-cinnamate was determined to be -12±2 cm³ mol⁻¹,⁵ i.e. it can be expected that the reaction rate could be increased under high-pressure conditions.⁶ This result intrigued us and led us to examine the effect of high pressure on the reaction rate and enantioselectivity in the catalytic AD reaction. Herein, we report our preliminary results on the influence of high pressures on the osmium-catalyzed AD of trans-cinnamates, which revealed a substantial increase of the turnover number (TON) of the catalyst.⁷

To examine the high-pressure effect on osmium-catalyzed AD of alkenes, in terms of reactivity as well as enantioselectivity, we carried out AD reaction of transcinnamates 1a-c under homogeneous conditions^{8,9} using N-methylmorpholine N-oxide (NMO) as a cooxidant in acetone-H₂O (10:1). The AD products of 1a-c have already been successfully used as key intermediates for some pharmacologically active compounds, such as the side-chain of Paclitaxel,¹⁰ Diltiazem¹¹ and Chloramphenicol.¹² As shown in Table 1, experiments carried out under high pressure (entries 2, 5, 6, 8, 10, 12 and 14) clearly showed that the lifetime of the catalyst was dramatically prolonged. Experiments with 0.01 mol% of osmium catalyst under normal pressure (entries 3, 4, 9 and 13) revealed that the maximum TON for the osmium catalyst is 1900 (19% yield, entry 4). However, under high pressure (10 kbar, entries 5, 6, 10 and 14), the TONs increased up to 7800 (entry 10). To the best of our knowledge, this is the highest TON value ever reported in osmium-catalyzed AD. The observed increase in turnover number under high-pressure conditions could be attributed to the stabilization of catalyst by strongly enforcing coordination of chiral ligand to osmium. However, the enantioselectivity was decreased under 10 kbar, which might be ascribed to a too compact conformation of Os-complex, in which the substrates cannot fit in binding clefts well.¹³ On the other hand, experiments carried out under 20 bar using 0.05 mol% of osmium catalyst gave useful results. Under 20 bar, the AD reaction proceeded still much faster than under normal pressure, and e.e. was retained (compare the results of entries 2, 8 and 12 with those of entries 1, 7 and 11).

In conclusion, we have demonstrated that high pressure might be used in the catalytic AD reaction of *trans*-cin-

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Table 1. Asymmetric dihydroxylation of trans-cinnamate derivatives



Entry ^a	Substrate	OsO4 (mol%)	Pressure (bar)	Time (h)	Yield ^b (%)	TON ^c	% E.e. ^d	Config. ^e
1	1a	0.05	1	48	34	680	96.2	2 <i>R</i> ,3 <i>S</i>
2	1a	0.05	20	48	72	1440	96.1	2R, 3S
3	1a	0.01	1	24	13	1300	94.1	2R, 3S
4	1a	0.01	1	168	19	1900	94.1	2R, 3S
5	1a	0.01	10^{4}	24	26	2600	85.5	2R, 3S
6	1a	0.01	104	168	44	4400	85.0	2R, 3S
7	1b	0.05	1	48	73	1460	97.0	2R, 3S
8	1b	0.05	20	48	82	1640	97.3	2R, 3S
9	1b	0.01	1	168	12	1200	96.1	2R, 3S
10	1b	0.01	104	168	78	7800	91.1	2R, 3S
11	1c	0.05	1	48	67	1340	95.5	2R, 3S
12	1c	0.05	20	48	89	1780	96.0	2R, 3S
13	1c	0.01	1	168	12	1200	95.8	2R, 3S
14	1c	0.01	10^{4}	168	75	7500	81.2	2 <i>R</i> ,3 <i>S</i>

^a All reactions were carried out on a 1 mmol scale using 1.25 mol% of (DHQ)₂PHAL.

^b Isolated yields by column chromatography.

^c Turnover number.

^d % E.e.s of products were determined by chiral HPLC analysis.

e Absolute configurations were determined by comparison of physical data with those of authentic compounds.

namates as a tool to increase the turnover number of the catalyst. Further investigations to explore the effects of high pressure in asymmetric catalysis are currently under way.

Representative procedure of AD reactions under highpressure conditions (10 kbar): A solution of (DHQ)₂PHAL (9.7 mg, 0.0125 mmol), NMO (175.7 mg, 1.5 mmol) and aqueous solution of OsO_4 (7 µL, 0.155 mmol/L, 0.1 μ mol) in acetone–water (10/1, v/v, 3 mL) was transferred by syringe into a Teflon capsule. A solution of *iso*-propyl *trans*-4-methoxycinnamate 1b (220.3 mg, 1.0 mmol) in acetone-water (2 mL) was added to the mixture by means of syringe and cooled to -78°C before the AD reaction to prevent any further reaction. After the Teflon cell was sealed, it was placed in an autoclave, where the AD reaction was performed without stirring at 10°C under pressure (10 kbar). After 168 h, the reaction was quenched with Na₂SO₃ solution. The organic material was extracted three times with ethyl acetate, and the combined extracts were dried with Na₂SO₄. After evaporation of the solvent, the crude product was purified by chromatography on silica gel to give the diol **2b** (198.3 mg, 78%). E.e. = 91.1%.

Representative procedure of AD reactions under elevated pressure conditions (20 bar): In a 30 mL steel autoclave, equipped with a magnetic stirrer and a glass inline, $(DHQ)_2PHAL$ (9.7 mg, 0.0125 mmol), NMO (175.7 mg, 1.5 mmol) and an aqueous solution of OsO₄ (35 μ L, 0.155 mmol/L, 0.5 μ mol) were dissolved in a solu-

tion of methyl *trans*-cinnamate **1a** (162.2 mg, 1.0 mmol) in acetone–water (10 mL). Then the autoclave was closed, pressurized with nitrogen, and stirred. After 48 h, the reaction mixture was worked-up as described above to yield 141.3 mg (72%) of the diol **2a** (96.1% e.e.).

The e.e.s of products **2a–c** were determined by chiral HPLC. For **2a**: Chiralcel OJ, *iso*-PrOH/hexane (1/4), 1.0 mL min⁻¹; 11.7 min (2*R*,3*S*), 17.6 min (2*S*,3*R*). For **2b**: Chiralpak AD, *iso*-PrOH/hexane (15/85), 1.0 mL min⁻¹; 17.8 min (2*S*,3*R*), 20.3 min (2*R*,3*S*). For **2c**: Chiralpak AD, *iso*-PrOH/hexane (1/4), 1 mL min⁻¹; 14.9 min (2*S*,3*R*), 21.5 min (2*R*,3*S*).

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- 7. We also carried out the AD reactions of other olefins, such as 1-phenylcyclohexene and *trans*- β -methyl styrene, using NMO as a co-oxidant under high pressure. However, in contrast to *trans*-cinnamates, we could not find any substantial increase in TON.

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- The following results may provide indirect evidence of this argument. In contrast to the results attained under normal pressure, the e.e.s of 2a obtained under high-pressure AD conditions were increased by increasing the reaction temperature (reaction conditions: 1 mol% of K₂OsO₂(OH)₄, 1.25 mol% of (DHQ)₂PHAL), 10 kbar: 84% e.e. (10°C), 90% e.e. (20°C), 92% e.e. (30°C) and 93% e.e. (40°C); cf. 1 bar: 96% e.e. (10°C), 94% e.e. (20°C), 91% e.e. (30°C) and 84% e.e. (40°C)).