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Highly enantioselective osmium dihydroxylation of unsubstituted allyl *N*-phenylcarbamate using AD-*mix* reagents

Etsuko Kawashima,[a,*] Yuh-ki Naito [a] and Yoshiharu Ishido [b]

[a] *Laboratory of Pharmaceutical Chemistry, School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan*

[b] *Department of Chemistry, Division of Natural Sciences, College of Liberal Arts, International Christian University, 3-10-2 Oh-sawa, Mitaka, Tokyo 181-0015, Japan*

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Abstract

A prominent effect of the phenylcarbamoyl protecting group on the asymmetric dihydroxylation (AD) reaction was confirmed in both of the reactions of allyl *N*-phenylcarbamate with AD-*mix*-α and -β, bringing about excellent enantioselectivity (>99% *ee*) to give (*R*)- and (*S*)-glycerol 1-(*N*-phenylcarbamate) in quantitative yields, respectively.

Keywords: asymmetric synthesis; hydroxylation; enantioselection; glycerol.

Chiral glyceraldehyde derivatives are versatile substrates for the synthesis of optically active target molecules.[1] They are characterized by the ready availability of both enantiomers from natural sources, and by a pronounced versatility due to the presence of the aldehyde and diol functionality in the molecule. If a highly enantioselective glycerol derivative could be obtained from an *O*-protected allyl alcohol, the chemistry should potentially lead us to excellent intermediates in stereoselective organic synthesis,[1] because chiral glycerol derivatives are easily convertible to chiral glyceraldehyde derivatives.

The synthesis of a chiral glycerol derivative by the use of the reaction of an *O*-protected allyl alcohol derivative with AD-*mix* was reported by Sharpless et al.[2] and Corey et al.[3] Sharpless et al.[2] demonstrated that allyl 4-substituted phenyl ethers are excellent substrates for the reaction with AD-*mix*-β to give enantioselectivities ranging from 89 to 95% ee. On the other hand, Corey et al.[3] claimed that the 4-methoxybenzoyl group at the terminal hydroxyl group of the resulting chiral glyceryl ester is specifically advantageous for suppressing the acyl migration reaction, as compared to an acetyl or benzoyl group, to give excellent enantioselectivity (98% ee) by the use of a similar biscinchona alkaloid ligand involving a pyridazine connector. To minimize the extent of acyl migration to the newly introduced hydroxyl groups of the product, however, a modified set of dihydroxylation conditions had to be employed, and product isolation must be performed immediately upon completion of the reaction as indicated by TLC analysis.[3]

Incidentally, the authors experienced excellent diastereoselectivity in the dihydroxylation reaction[4] of 2,3-di-*O*-benzyl-4,5-didehydro-4,5-dideoxy-D-[5-^{13}C]ribose dibenzyl acetal with osmium tetroxide–

* Corresponding author. Tel: +81 426 76 3074; fax: +81 426 76 3073; e-mail: kawasima@ps.toyaku.ac.jp (E. Kawashima)

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Table 1
AD reactions of *O*-protected allyl alcohols **1** and **2**

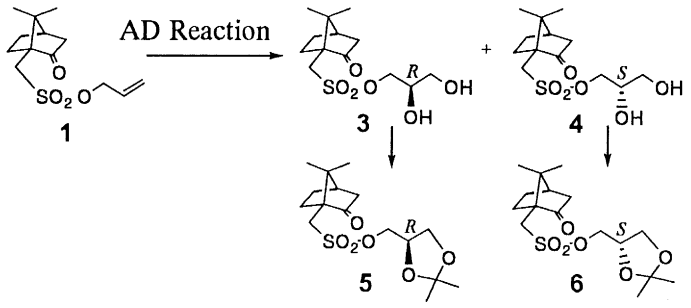
Entry	Substrate	Reagents	Temp. (℃)	Time (h)	Yield (%)	% de(*) % ee
1	**1**	OsO_4 (0.05 mol equiv.) 4-Methylmorpholine *N* -oxide (2 mol equiv.) H_2O-Acetone	r.t.	24	66	0*
2	**1**	$K_2OsO_2(OH)_4$ (0.2 mol %) $K_3Fe(CN)_6$ (3 mol equiv.) , K_2CO_3 (3 mol equiv.) DHQ-PHN (2 mol %) *t* -BuOH-H_2O	0	24	13	40*
3	**1**	AD-*mix* -β *t* -BuOH-H_2O	0	20	64	30*
4	**2**	OsO_4 (0.05 mol equiv.) 4-Methylmorpholine *N* -oxide (2 mol equiv.) H_2O-Acetone	r.t.	24	61	0
5	**2**	AD-*mix* -α *t* -BuOH-H_2O	0	18	99 (mp 85 ℃)	>99 (*R*)
6	**2**	AD-*mix* -β *t* -BuOH-H_2O	0	18	99 (mp 85 ℃)	>99 (*S*)

The yields are of the products obtained by the osmium AD reaction.
The % de (* mark) and % ee values of the products in Entries 1 – 6 were determined by 400 MHz ^{1}H-NMR spectroscopy after transforming each product into **5** and **6**, in addition, in Entries 5 and 6 by ^{19}F NMR spectroscopy, after transforming each product into **9** and **10** by MTPA ester formation reaction.

4-methylmorpholine *N*-oxide[5] without the biscinchona alkaloid ligand, giving a 93:7 mixture of D-*ribo* and L-*lyxo* isomers in 97% total yield. It can be presumed that the excellent diastereoselectivity is attributable to the steric hindrance of the benzyl groups at the 2 and 3 positions.

In view of the above background, we undertook an investigation of the AD reaction of an *O*-protected allyl alcohol.

In the first stage, we tried a reaction of allyl (1*S*)-(+)-camphor-10-sulfonate (**1**) bearing a large protecting group with osmium tetroxide–4-methylmorpholine *N*-oxide. Since the results showed no diastereoselectivity (Entry 1), the conditions used by Sharpless et al.[6,7] were examined. The results obtained are summarized in Table 1 together with the conditions used. The dihydroxylation products, (*R*)-glycerol 1-((1*S*)-(+)-camphor-10-sulfonate) (**3**) and the corresponding (*S*)-isomer (**4**), in Entries 1–3 were subjected to isopropylidenation as usual, and % *de* values were determined by calculation of the area ratios of geminal *H*-10 signals (δ 3.05 and 3.65 ppm for (*R*)-isomer; δ 3.06 and 3.64 ppm for (*S*)-isomer) of the camphor-10-sulfonyl moiety of (*R*)-2,3-*O*-isopropylidene [glycerol 1-(1*S*)-(+)-



Scheme 1.

camphor-10-sulfonate] (**5**)[8] and the corresponding (*S*)-isomer (**6**)[8] in the resulting mixtures (Scheme 1). No excellent diastereoselectivity was obtained among the reactions in Entries 1–3 in spite of the introduction of the large protecting group.

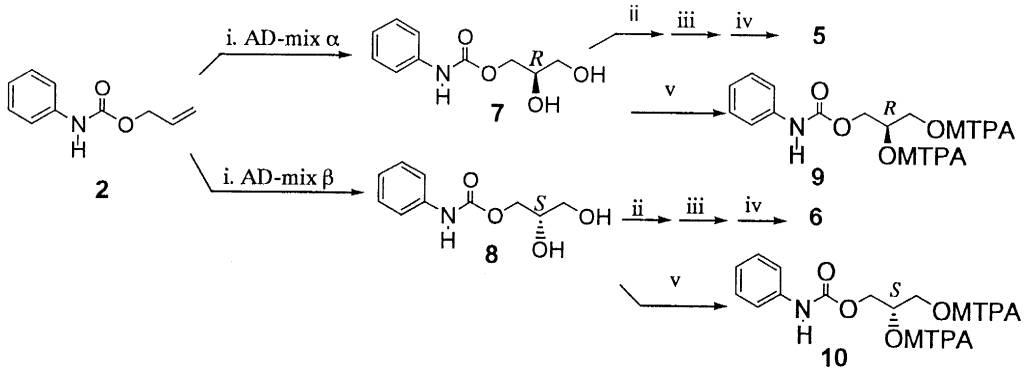
Incidentally, the authors recently participated in the development of novel efficient methods for the unmasking of alkyl *N*-phenylcarbamates.[9] Another characteristic aspect of the reaction is the role expected of a phenylcarbamoyl group as the protecting group of allyl alcohol in the AD reaction, namely, that it can serve to differentiate the original allylic hydroxyl group from those introduced in the dihydroxylation step with much less tendency to undergo oxygen-to-oxygen acyl rearrangement as compared to the 4-methoxybenzoyl group reported by Corey et al.[3] We should thus be able to perform the reaction without having to pay attention to minimizing the reaction time. Moreover, the use of the phenylcarbamoyl group as the protecting group of allyl alcohol is expected to give chiral glycerol derivatives with high enantioselectivity, because it can be presumed that the phenylcarbamoyl group with planar structure is held in U-shaped conformation of the biscinchona alkaloid ligand in the transition state reported by Corey et al.[3]

In the second stage, therefore, we undertook an investigation of the osmium-mediated asymmetric dihydroxylation reaction of allyl *N*-phenylcarbamate (**2**). We wish to communicate the results obtained herein, putting emphasis on the excellence of the phenylcarbamoyl protecting group in the enantioselective osmium dihydroxylation reaction in the manner reported by Sharpless et al.[7] The results obtained from the reaction are summarized in Table 1 together with the conditions used.

The determination of the % *ee* values of the dihydroxylation products, (*R*)-glycerol 1-(*N*-phenylcarbamate) (**7**) and the corresponding (*S*)-isomer (**8**), in Entries 4–6 was carried out in the same manner as for **3** and **4**, after transforming each product into **5** and **6** in three steps: isopropylidenation as usual, *O*-dephenylcarbamoylation,[9] and *O*-(1*S*)-(+)-camphor-10-sulfonylation, respectively.

In addition, the products in Entries 5 and 6 were converted into the corresponding bis-(*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetate (MTPA) esters [(*R*)-2,3-bis-*O*-MTPA-[glycerol 1-(*N*-phenylcarbamate)] (**9**)[8] and the corresponding (*S*)-isomer (**10**)[8]], in the manner reported by Dale et al.[10]

Their % *ee* values were calculated by the area ratios of ^{19}F signals of their MTPA moieties (δ −8.86 and −8.98 ppm for (*R*)-isomer ester and δ −8.78 and −8.87 ppm for (*S*)-isomer relative to an internal reference of α,α,α-trifluorotoluene at 376.5 MHz) in the resulting mixtures. The resulting % *ee* values from the MTPA method were exactly the same as those from the method of camphor-10-sulfonate derivatives **5** and **6**. It is noteworthy that both of the reactions of **2** using AD-*mix*-α and -β shown in Entries 5 and 6 gave **7** and **8** in quantitative yields with strikingly high enantioselectivities exceeding 99%, respectively (Scheme 2). A crucial factor for giving such excellent stereoselectivity might be the unique



Scheme 2. Reagents and conditions: (i) AD-*mix*-α or β, *t*-BuOH–H_2O, 0°C, 18 h, >99% *ee*, 99% yield, respectively, see Ref. 7; (ii) isopropylidenation as usual; (iii) *O*-dephenylcarbamoylation, see Ref. 9; (iv) *O*-(1*S*)-(+)-camphor-10-sulfonylation; (v) see Ref. 10

electronic structure of the phenylcarbamoyl protecting group arising from its easily moving electron pair on the nitrogen atom to the carbonyl oxygen atom.

Presumably, **2** might participate in the reaction with its *s-cis* conformation[3] and the reaction might thus proceed efficiently via the transition state, in which **2** is appropriately accommodated in the binding pocket between the biscinchona alkaloid ligand to bring about each of the chiral glycerol derivatives with high enantioselectivity, as has been discussed by Corey et al.[3] (Fig. 1).

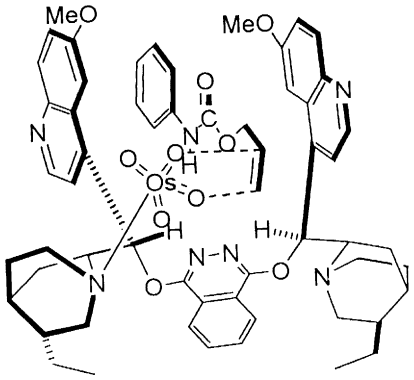


Fig. 1.

Therefore, the significant role of the phenylcarbamoyl protecting group in the asymmetric dihydroxylation reaction of the unsubstituted allyl alcoholic system using AD-*mix*-α and -β was confirmed to afford remarkably high enantioselectivity (>99% ee).

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References

1. Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447–488.
2. Wang, Z.-M.; Zhang, X.-L.; Sharpless, K. B. *Tetrahedron Lett*. **1993**, *34*, 2267–2270.
3. Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc*. **1994**, *116*, 12 109–12 110; *idem*., *ibid*. **1995**, *117*, 10 805–10 816.
4. Sekine, T.; Kawashima, E.; Ishido, Y. *Tetrahedron Lett*. **1996**, *37*, 7757–7760.
5. Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. *J. Am. Chem. Soc*. **1988**, *10*, 1968–1970.
6. Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1992**, *57*, 2768–2771.
7. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1991**, *56*, 4585–4588.
8. Authentic samples corresponding to those ester derivatives **5** and **6** were derived from commercially available (*R*)- and (*S*)-1,2-*O*-isopropylidene glycerol, purchased from Aldrich Co., by the reaction with camphor-10-sulfonyl chloride in pyridine. Those of **9** and **10** were by the treatments in turn with phenyl isocyanate in pyridine, with 2 M HCl aq. at 80°C for 4 h, and finally with MTPA chloride in pyridine.
9. Akai, S.; Nishino, N.; Iwata, Y.; Hiyama, J.; Kawashima, E.; Sato, K.; Ishido, Y. *Tetrahedron Lett*. **1998**, *39*, 5583– 5586.
10. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc*. **1973**, *95*, 512–519.