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Stereocontrolled preparation of 1,2-diol with quaternary chiral center

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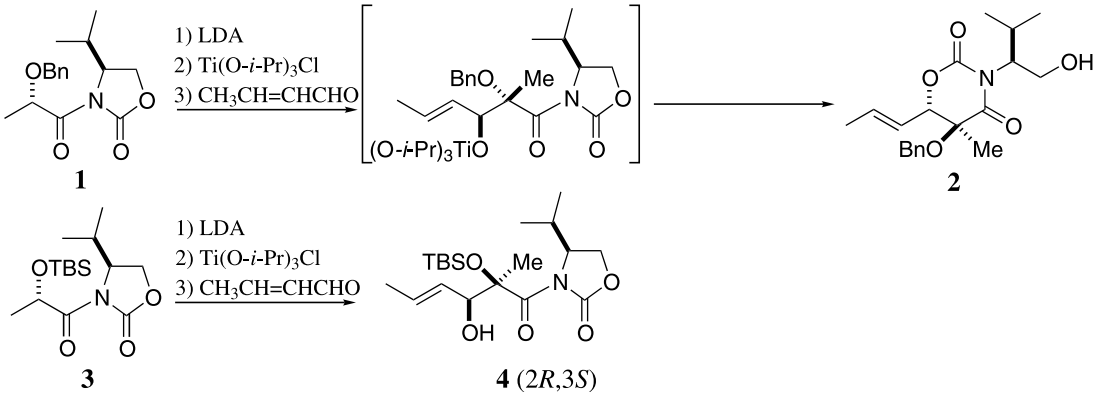
Abstract—Development of an enantio- and stereoselective construction of 1,2-diols including a quaternary chiral center was achieved by a titanium-mediated aldol reaction of lactates bearing chiral oxazolidine-2-ones. *anti*-Aldol and *syn*-aldol were selectively obtained by the choice of a benzyl and TBS protecting group, respectively. Plausible transition states are also shown based on the stereochemistry of the enolate anion. © 2002 Elsevier Science Ltd. All rights reserved.

1,2-Diol unit including a quaternary chiral center is seen in many natural products such as macrolide and polyether antibiotics, and the stereocontrol of this functionality is an interesting subject in organic synthesis.[1] One most practical methodology is an enantioselective dihydroxylation of substituted olefin developed by Sharpless et al.[2] High enantioselectivity is generally attained for the preparation of a *syn*-diol, however, relatively low e.e. is observed in the case of an *anti*-diol. Further, stereoselective construction of the substituted olefin is needed prior to the enantioselective dihydroxylation, and thus the development of a general and highly stereoselective methodology is still demanded.[3] We recently reported a stereoselective aldol reaction of the titanium enolate generated from a lactate derivative bearing Evans' chiral auxiliary.[4] We also observed that the stereochemical course of the aldol reaction was found to differ depending on the protective group of the hydroxy group as shown in Scheme 1.[4,5] However, this methodology is not suitable for the preparation of an *anti*-aldol because the resulting adduct underwent a simultaneous cyclization affording the ketocarbamate **2** which requires a forced condition for hydrolysis. In this paper we describe an improvement of the methodology by employing the SuperQuats[6] instead of Evans' chiral auxiliary.

SuperQuats derivative **5** was prepared from (*S*)-benzyloxypropionic acid and the corresponding SuperQuats derived from L-valine. In a similar manner to the case of **1**, SuperQuats **5** was treated with LDA followed by $TiCl(O\text{-}i\text{-}Pr)_3$, and the resulting titanium enolate was



Scheme 1.

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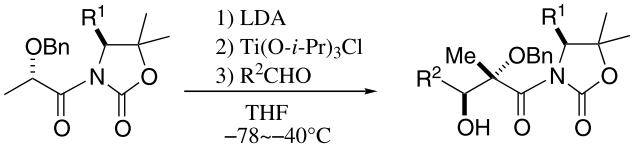
then reacted with crotonaldehyde. Different from the previous case, aldol adduct **6** was isolated in 96% yield in the present reaction, and none of the recyclized ketocarbamate was formed.[7] Stereoselectivity of the reaction is high, affording the *anti*-aldol **6** and *syn*-aldol **7** in a ratio of 11:1. Stereochemistry of the *anti*-aldol **6** was unambiguously established by correlating to the stereochemically established acetonide **9** via diol **8**, and the minor isomer **7** was tentatively assigned as shown in analogy to the case of Evans' oxazolidine-2-one **1** (Scheme 2).[4] Encouraged with this result, SuperQuats (**10** and **12**) were prepared from the corresponding chiral oxazolidine-2-ones derived from L-phenylalanine and D-phenylglycine, respectively. Then the titanium-mediated aldol reactions with crotonaldehyde, isobutyraldehyde, and hexanal were examined. The results are summarized in Tables 1 and 2. As shown in Tables 1 and 2, both enantiomers of the *anti*-diols (2*S*,3*S*-**11** and 2*R*,3*R*-**13**) were obtained with excellent stereoselectivities. It should be mentioned again that ketocarbamates were not formed by employing SuperQuats.

Although the *t*-butyldimethylsilyl lactate derivative with Evans' oxazolidine-2-one afforded the *syn*-aldol without accompanying formation of undesirable ketocarbamate (preparation of (2*R*,3*S*)-**4** in Scheme 1), the aldol reaction of the corresponding SuperQuats **14** was also examined. As expected, *syn*-aldol (2*S*,3*R*)-**15** was obtained in high yield and stereoselectivity (91% yield and >10:1 selectivity) as shown in Scheme 3.

Thus both relative and absolute stereocontrol of the 1,2-diol with a quaternary chiral center became possible by the choice of the protecting groups (TBS or benzyl) and appropriate chiral oxazolidine-2-ones. Additionally, it should be noted that aldol adducts were afforded with protected tertiary alcohol.

In order to understand the stereochemical course of the reaction, trapping of the enolate was next attempted. The enolate anion derived from benzyl-protected SuperQuats **12** was treated with TESCl to afford the silyl enol ether **16** in 70% yield as a single isomer. Stereochemistry of the *E*-*O*-enolate of **16** was determined by NOE experiment. In contrast, generation of the *Z*-*O*-enolate from TBS-protected SuperQuats **14**

Table 1. Preparation of (2*S*,3*S*)-diol



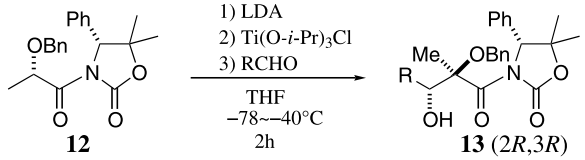
5 : R^1=*i*-Pr

10 : R^1=$PhCH_2$

11 (2*S*,3*S*)

Entry	R^1	R^2	Yield (%)	Selectivity
1	*i*-Pr	CH_3CH=CH	96	11:1
2	*i*-Pr	$(CH_3)_2CH$	94	>99:1
3	*i*-Pr	$CH_3(CH_2)_3CH_2$	85	>99:1
4	$PhCH_2$	CH_3CH=CH	96	11:1
5	$PhCH_2$	$(CH_3)_2CH$	94	14:1
6	$PhCH_2$	$CH_3(CH_2)_3CH_2$	85	>99:1

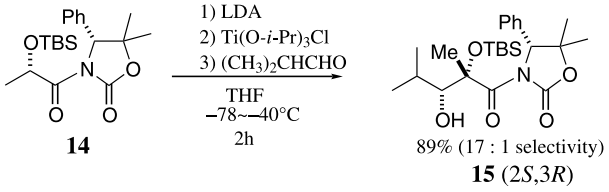
Table 2. Preparation of (2*R*,3*R*)-diol



12

13 (2*R*,3*R*)

Entry	R	Yield (%)	Selectivity
1	CH_3CH=CH	85	24:1
2	$(CH_3)_2CH$	96	57:1
3	$CH_3(CH_2)_3CH_2$	93	>99:1

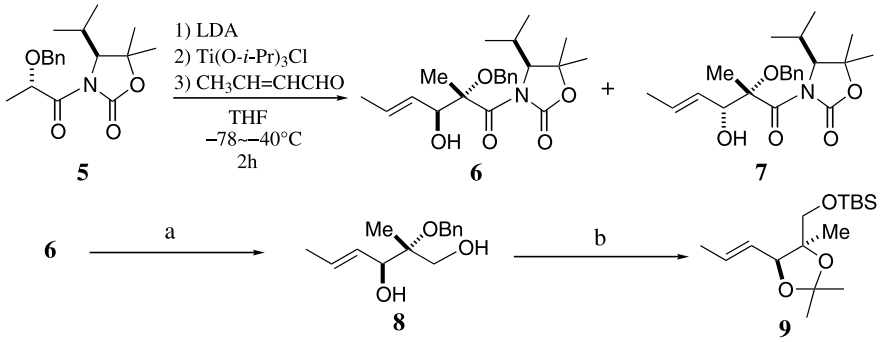


14

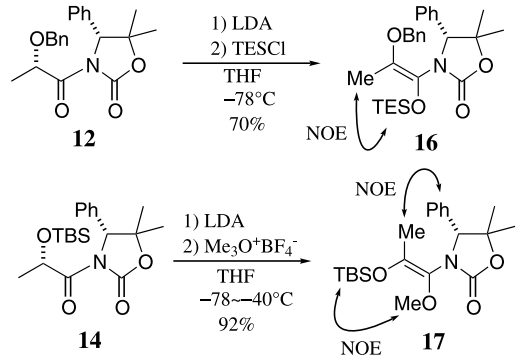
89% (17 : 1 selectivity)

15 (2*S*,3*R*)

Scheme 3. Preparation of (2*S*,3*R*)-diol.



Scheme 2. *Reagents and conditions:* (a) (i) BnOH, BuLi, THF, –20°C, 72%; (ii) LAH, THF, 71%; (b) (i) TBSCl, *i*-Pr_2NEt, DMAP, CH_2Cl_2, 70%; (ii) Li, NH_3, 64%; (iii) dimethoxypropane, CSA, CH_2Cl_2, 91%.



Scheme 4. Trapping of enolate by silylation or alkylation.

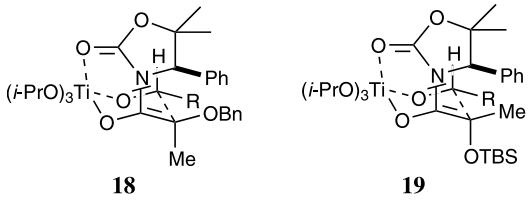


Figure 1.

was confirmed by NMR study of isolated **17**. Thus, NOE was observed between OMe and *t*-BuMe$_2$Si. NOE between olefinic Me and Ph was also observed (Scheme 4).[8] Although the precise mechanism is not clear, we assume that the *E*-*O*-enolate is thermodynamically favored considering an electronic repulsion between the α-alkoxyl group and the enolate anion, thus affording *E*-*O*-enolate **16** in the case of benzyloxy derivative **12**. On the other hand, the selective formation of *Z*-*O*-enolate **17** might be due to the serious steric repulsion between the TBS group and the oxazolidine moiety in the *E*-*O*-enolate.

Based on these results, plausible transition states of the present titanium-mediated aldol reaction are shown in Fig. 1. Thus, carbonyl oxygen of the oxazolidine-2-one coordinates to titanium, and an aldehyde approaches from the less hindered side (opposite to the phenyl group in **18** and **19**). Both relative and stereochemical course of the present aldol reaction could be rationally explained by transition states **18** and **19**.

In conclusion, we were able to develop a general and stereoselective route to 1,2-diols including a quaternary chiral center. Particularly noteworthy is that all the chiral center could be controlled by the proper choice of a protecting group and an oxazolidin-2-one. The present methodology could be applicable to the synthesis of various biologically interesting compounds, and further studies along this line are now in progress.

Acknowledgements

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References

1. *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G.; Ohno, M., Eds.; Springer: Berlin, 1990.
2. Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785–3786.
3. Corey, E. J.; Jardine, P. D.; Virgil, S.; Yuen, P.-W.; Connell, R. D. *J. Am. Chem. Soc.* **1989**, *111*, 9243–9244.
4. Kamino, T.; Murata, Y.; Kawai, N.; Hosokawa, S.; Kobayashi, S. *Tetrahedron Lett.* **2001**, *42*, 5249–5252.
5. Mukaiyama et al. also reported a similar stereocontrolled preparation of *syn*- and *anti*-1,2-diol by choice of the protecting group of the *E*-*O*-enolate derived from glycolic acid. Benzyloxy derivative afforded an *anti* isomer through the coordination of the benzyloxy group to a Lewis acid, whereas the *t*-butyldimethylsiloxy derivative gave a *syn* isomer through an extended transition state. Therefore, the aldol reaction proceeds in a stereoselective manner regardless the stereochemistry of an enolate; Mukaiyama, T.; Shiina, I.; Uchiro, H.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1708–1716.
6. Davies, S. G.; Sangnee, H. J.; Szolcsanyi, P. *Tetrahedron* **1999**, *55*, 3337–3354.
7. General procedure: To a solution of LDA (prepared from DIPA (46.7 μl, 356 μmol), and BuLi (2.6 M in hexane, 129 μl, 335 μmol) at −78°C for 15 min) was added a solution of **5** (71.1 mg, 223 μmol) at −78°C. After stirring for 30 min at −78°C, Ti(O-*i*-Pr)$_3$Cl (1.0 M in hexane, 0.89 ml, 892 μmol) was added and the resulting mixture was stirred for 1 h at −40°C. After cooling to −78°C, crotonaldehyde (21.6 μl, 268 μmol) was added to the mixture which was additionally stirred at −40°C for 2 h. The reaction mixture was quenched with satd NH_4Cl and stirred with Celite for 1 h at rt. Filtration and evaporation gave a crude oil, which was purified by column chromatography (hexane:AcOEt = 10:1) to yield **6** (71.1 mg, 88%) and **7** (6.4 mg, 8%). **6**: R_f = 0.43 (hexane:AcOEt = 2:1); $[\alpha]_D^{23}$ +33.7 (*c* 2.11 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.98 (3H, d, *J* = 7.0 Hz), 1.02 (3H, d, *J* = 6.7 Hz), 1.32 (3H, s), 1.48 (3H, s), 1.67 (3H, dd, *J* = 1.2, 6.4 Hz), 1.79 (3H, s), 2.12–2.16 (1H, m), 3.67 (bs, 1H), 4.26 (1H, d, *J* = 3.7 Hz), 4.58 (1H, d, *J* = 10.4 Hz), 4.63 (1H, d, *J* = 10.7 Hz), 4.89 (1H, t, *J* = 7.3 Hz), 5.62 (1H, ddd, *J* = 1.53, 8.2, 15.4 Hz), 5.77 (1H, dq, *J* = 6.4, 15.6 Hz), 7.26–7.41 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 17.0, 17.6, 17.7, 21.2, 21.5, 28.3, 30.0, 66.3, 68.2, 74.4, 82.6, 86.6, 127.4, 127.5, 128.2, 129.5, 129.6, 138.1, 152.5, 173.0; IR (neat) 3518, 2976, 1778, 1695, 1497, 1359, 1125, 971, 735, 698; HR-FABMS: calcd for $C_{22}H_{32}O_5N$ ($[M-H]^+$) 389.2281, found 389.2286.
8. **16**: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.76 (6H, q, *J* = 1.95 Hz), 0.88 (3H, s), 1.00 (9H, t, *J* = 1.94 Hz), 1.48 (3H, s), 4.76 (1H, d, *J* = 11.0 Hz), 4.81 (1H, s), 4.89 (1H, d, *J* = 11.0) 7.25–7.45 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 4.86, 6.72, 13.15, 23.80, 27.49, 69.68, 71.02, 81.71, 127.54, 127.63, 127.75, 128.16, 128.24, 128.24, 128.26, 134.79, 136.46, 137.96, 155.49. **17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.00 (3H, s), 0.12 (3H, s), 0.98 (9H, s), 1.15 (3H, s), 1.97 (3H, s), 3.52 (3H, s), 4.85 (1H, s), 7.31–7.50 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) −5.21, −4.76, 17.98, 18.34, 23.69, 25.53, 27.97, 58.06, 69.00, 81.74, 127.71, 128.39, 128.58, 131.68, 134.67, 136.65, 155.88.