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The Effect of Water and Phenol on the Chiral Oxazaborolidine-Catalyzed Reduction of a Prostaglandin Enone Derivative

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Abstract:

The alcohol 2, a key intermediate in the synthesis of the highly selective EP4-receptor agonist ONO-4819, was synthesized by (*R*)-methyloxazaborolidine ((*R*)-Me-CBS)-catalyzed asymmetric reduction of enone 1 with borane dimethylsulfide complex. Addition of water and phenol to the reduction of enone 1 using (*R*)-Me-CBS as catalyst changed the chemoselectivity of the reduction.

Introduction

Prostaglandins have been shown to have a broad range of biological activities in diverse tissues through binding to specific receptors.[1] In particular, those of the E series are multifunctional regulators of bone metabolism.[2] Recently, it was reported that the highly selective agonist for prostaglandin E receptor subtype EP4 **ONO-4819** in combination with risedronate could be an effective treatment for osteoporosis.[3]

One of the key steps in the synthesis of **ONO-4819** is stereoselective reduction of enone **1** to chiral alcohol **2** (Scheme 1). We report here that addition of water and phenol changed chemoselectivity in the synthesis of key (*S*)-hydroxy intermediate **2** catalyzed by (*R*)-methyloxazaborolidine ((*R*)-Me-CBS).

Results and Discussion

The asymmetric reduction of carbonyl compounds with binaphthol-modified lithium aluminum hydride (BINOL-H) and chiral methyloxazaborolidine catalysts (CBS) has been demonstrated as a powerful tool for the synthesis of enantiomerically pure alcohols from prochiral ketones.[4,5] Initially, we demonstrated the reduction of **1** with stoichiometric amounts of BINOL-H reagent and obtained **2** with good diastereoselectivity (80% de), but these reduction conditions required improvement for scale-up (stoichiomeric amount of chiral reagent, tedious removal procedure for Al, and low concentration conditions were needed). Two unique structural features of enone **1** are worth noting: (a) the lactone moiety in the system of two 5-membered rings; (b) enone **1** has four chiral centers, one of which may affect the stereoselectivity for the reduction of the carbonyl moiety. We next screened the conditions of stereoselective reduction using Me-CBS catalyst with borane dimethysulfide complex (BMS), and the results are summarized in Table 1. Reduction of **1** with BMS in the presence of (*R*)-Me-CBS as a catalyst provided (*S*)-chiral alcohol **2** with moderate enantioselectivity (75% de, entry 1). As an earlier report had already mentioned that the enantioselectivity was enhanced by

Scheme 1

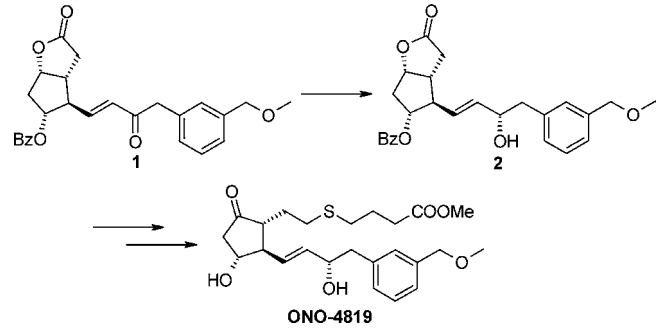
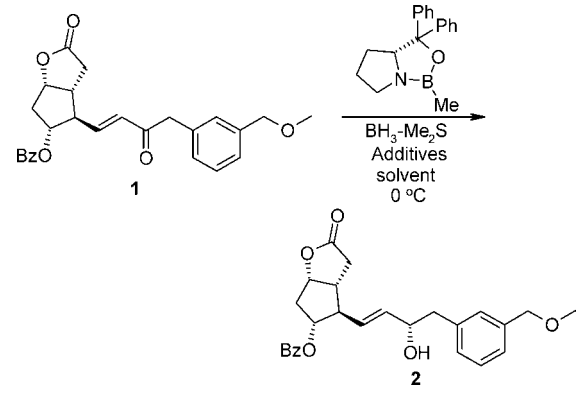


Table 1. **Screening of the stereoselective reduction of 1[a]**



entry	PhOH equiv	solvent	**2** yield %[b]	**2** de %
1	none	toluene	65	75
2	1.0	toluene	95	80
3[c]	1.0	toluene	85	62
4	none	THF	80	75
5	1.0	THF	85	45

[a] All reactions were conducted using the general procedure unless otherwise noted. To the mixture of BH_3-Me_2S (1 equiv), phenol and (*R*)-Me-CBS catalyst (0.1 equiv) at 0 °C was added a solution of **1** over 10 min. [b] The combined yield of (*S*)- and (*R*)-alcohols was determined by HPLC using an absolute calibration method. [c] BH_3-Me_2S was added to the mixture of **1**, catalyst, and phenol in toluene.

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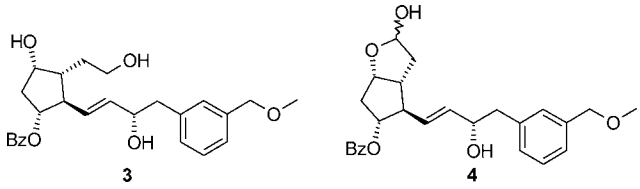

Figure 1

Table 2. **Effect of water for chemoselectivity on reduction of enone 1**[a]

entry	BMS equiv	H_2O equiv	time[b] h	HPLC area ratio 1	2	3	4
1[c]	5.0	none	0	2.8	95.9	0.07	0.6
			3	0	2.6	71.1	26.2
2[c]	5.0	0.2	0	74.9	23.2	1.1	0.8
			3	2.2	92.7	3.7	1.4
3[d,e]	1.0	0.1	5	3.5	95.1	1.2	0.3

[a] All reactions were conducted using the general procedure unless otherwise noted. To the mixture of BH_3-Me_2S, phenol, catalyst, and H_2O in toluene was added enone **1** at 0 °C over 10 min. [b] Reaction time after completion of adding enone **1**. [c] 5 equiv of phenol and 0.5 equiv of catalyst were used. [d] 1 equiv of phenol and 0.1 equiv of catalyst were used. [e] **1** was added over 2.5 h.

using alcohol as additives for this reduction,[6] addition of phenol slightly increased the stereoselectivity in toluene (entry 2). These two results described above were obtained by slow addition of enone **1** into a premixed solution of BMS, phenol and catalyst. It is good to mention that the stereoselectivity was decreased to 62% de when BMS was added to the mixture of enone **1** and catalyst (entry 3). We also need to note that addition of phenol sometimes caused negative impact on the stereoselectivity, for example, the reduction in THF media which you can find the results in entries 4 and 5. From these initial experiments, we decided to select the entry 2 condition in Table 1 for further optimization work for a scale-up in the reduction of **1**.

In a small-scale experiment, an extended addition time of **1** caused no problems for the reaction based on the selected conditions. However, a kilogram lab-scale synthesis (**1**, 769 g) led to overreduction of the lactone moiety on **1** to give a substantial amount (~30%) of triol **3** and lactol **4** (Figure 1) without completion of the desired ketone reduction. To overcome this chemoselectivity issue, we investigated the effect of the addition period of **1** to the reaction mixture, temperature, and purity of catalyst, but no difference was observed in the reduction of lactone moiety of enone on a smalll scale (~3% of triol **3** and lactol **4**).

It is thought that the reductant was in excess to **1** at an early stage of the addition period of enone **1**, so we decided to examine the effect of addition of water in the condition that a larger excess of BMS and catalyst were used (Table 2). Almost all the lactone moiety was reduced to triol **3** and lactol **4** in the presence of large amount of reducing reagent (entry 1) in anhydrous condition. Ordinarily, it is important to keep the reaction mixture under anhydrous conditions due to the sensitivity of the (*R*)-MeCBS catalyst, however, the reaction which was executed in the presence of 0.2 equiv of water in a solution containing a large excess of BMS, catalyst and PhOH improved the chemoselectivity to be controlled to 5.1% of triol **3** and lactol **4** (entry 2). Since we obtained satisfied results in the condition that large amount of reductant was present in the mixture, we applied this promising condition to the normal one. When addition period of **1** was extended in the presence of water, chemoselectivity was found to be improved (entry 3). Addition of 0.1 equiv of water led to formation of almost no overreductive byproducts and afforded (*S*)-chiral alcohol **2** with good stereoselectivity (77% de) even when **1** was added over 2.5 h.

Table 3. **Effect of water and phenol in the reduction of enone 1**[a]

entry	PhOH equiv	H_2O equiv	time h	HPLC area ratio 1	2	3	4	5	6	**2** de %
1	1.0	none	3	3.2	87.7	2.1	1.3	4.4	1.3	78
2	1.0	0.1	5	3.0	82.0	1.0	0.3	9.4	4.3	77
3	1.1	none	4	ND[b]	71.2	0.2	0.5	20.9	7.2	78
4	1.0	0.05	3	ND	98.3	0.7	0.1	0.7	0.2	80

[a] To the mixture of BH_3-Me_2S (1.0 equiv), phenol, catalyst (0.1 equiv) and H_2O in toluene was added **1** solution at 0 °C over 10 min. [b] ND: not detected.

We also found interesting chemoselectivity between 1,2- and 1,4-reduction of the enone moiety of **1** (Table 3). When 1.0 equiv of phenol was used in the absence of water in toluene, 5.7% of **5** and **6** was obtained, which was formed *via* 1,4- and 1,4- plus 1,2-reduction of the enone moiety of **1** (entry 1). Additional water promoted the 1,4-reduction of the enone moiety of **1** (entry 2). Using 1.1 equiv of phenol in the absence of water also increased the byproducts **5** and **6** (entry 3). However, addition of 0.05 equiv of water to the reaction mixture in the presence of 1.0 equiv of phenol decreased the formation of these byproducts **5** and **6**, and desired product **2** was obtained with good stereoselectivity. Also, the amount of triol **3** and lactol **4** was well controlled to less than 1% (entry 4). It is thought that adding alcohol to an oxazaborolidine-catalyzed reduction accelerates the recycling of the active catalyst species which leads to the improvement in stereoselectivity.[6a] In the reduction of enone **1**, addition of water and phenol led not only to the prevention of the reduction of the lactone moiety but also to the promotion of 1,4-reduction of the enone moiety. From these observations, although the reaction mechanism is unclear, the active reductant species is likely to be a soft hydride source compared to conditions involving no additives. Because slight difference of water equivalent affected the regioselectivity in the reduction of enone **2**, we kept the attention to the water content of the starting material **1** which was controlled no less than 0.05 wt % and the solvent was used as dehydrated grade in small-scale experiments. From the point of the purity of (*R*)-Me-CBS catalyst, the catalyst purchased from BASF showed good reproducibility in stereoselectivity and regioselectivity. For further scale-up manufacturing, we believe that water content of the reaction mixture should be controlled to the appropriate amount for a desired reaction since it is a very important factor for chemoselectivity of the reduction, and the evaluation in the case that addition period of reagents is extended should be conducted for the stereoselective reduction of high functionalized compound using Me-CBS catalyst with BMS.

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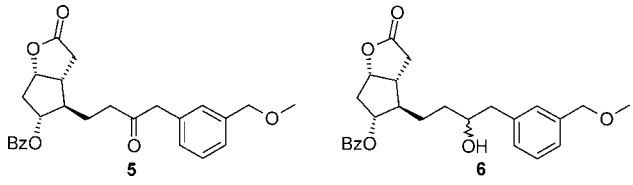

Figure 2

Conclusion

In conclusion, we have performed the stereoselective reduction of prostaglandin enone derivative using BMS in the presence of (*R*)-Me-CBS as a catalyst. In scale-up manufacturing of this reaction, a small amount of water was crucial to prevent the over-reduction of the lactone moiety. We also found interesting changes in chemoselectivity to be brought about by addition of water and phenol. The mechanism of changing chemoselectivity for the reduction in the presence of water remains unclear, and further studies are needed to understand the reaction pathway in detail.

Experimental Section

General. Infrared (IR) spectra were recorded on a Jasco FT-IR-430 spectrometer. ^{1}H NMR spectra were measured with a Varian Gemini-200 (200 MHz) spectrometer. The chemical shifts (δ) on ^{1}H NMR spectra were reported in parts per million relative to tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The optical rotations were measured with a JASCO DIP-1000 polarimeter. High-performance liquid chromatography (HPLC) was carried out using a Hitachi LC-Organizer, L-4000UV Detector, L-6200 Intelligent Pump, and D-2500 Chromato-Integrator or Shimazu LC-2010. Analytical TLC was performed on Merck preparative TLC plates (silica gel 60 F254, 0.25 mm). Column chromatography was carried out with silica gel [Fuji Silysia BW-235S]. All reactions were carried out under argon atmosphere unless otherwise noted.

Dehydrated solvents (THF and toluene) were purchased from Kanto Kagaku and were used as received. (*R*)-Methyl-CBS-oxazaborolidine toluene solution (1.0 mol/L) was purchased from BASF.

Preparation of (3a*R*,4*R*,5*R*,6a*S*)-4-{(1*E*,3*S*)-3-hydroxy-4-[3-(methoxymethyl)phenyl]-1-buten-1-yl}-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-5-yl Benzoate 2. To a mixture of phenol (3.25 g, 34.5 mmol) and water (31 mg, 1.73 mmol) in toluene (30 mL) was added BH_3-Me_2S (3.28 mL, 34.5 mmol) at room temperature. The resulted mixture was stirred for 30 min. Then (*R*)-Me-CBS catalyst (1.09 mol/L in toluene, 3.45 mL, 3.45 mmol) was added at 0 °C, and the mixture was stirred for another 30 min. To the mixture was added enone **1** (15 g, 34.5 mmol) in toluene (75 mL), and stirring was continued at 0 °C. After stirring for 1.5 h, to the solution was added MeOH (7.0 mL, 172.5 mmol) and aq 15% NH_4Cl solution (150 mL), and the resulted mixture was stirred for 30 min at room temperature. The separated aqueous layer was extracted with toluene (30 mL), and the combined organic layers were washed with aq 20% NaCl solution (30 mL) and dried over anhydrous $MgSO_4$. The solvent was removed by evaporation, and the residue was purified by column chromatography on silica gel (Fuji silysia BW-235S, 557 g, toluene/EtOAc = 3:2) to give **2** as a colorless oil (11.8 g, 79%, 90.2% de, 99.3 area %). R_f 0.34 (hexane/EtOAc, 1:2); $[\alpha]^{20}_D$ −35.2 (*c* 1.04, EtOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.00 (dd, 2H, J = 8.42, 1.28 Hz), 7.59 (m, 1H), 7.57 (m, 1H), 7.45 (m, 2H), 5.55 (ddd, 1H, J = 15.47, 7.23, 1.10 Hz), 5.20 (m, 1H), 5.03 (td, 1H, J = 6.50, 1.83 Hz), 4.42 (s, 2H), 4.35 (m, 1H), 3.40 (s, 3H), 2.78 (m, 5H), 2.51 (m, 2H), 2.21 (ddd, 1H, J = 15.52, 4.90, 1.92 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.5, 166.1, 138.6, 137.7, 135.0, 133.4, 129.7, 129.6, 129.0, 128.92 (2C), 128.88 (2C), 128.6 (2C), 83.4, 79.3, 74.7, 72.9, 58.4, 54.0, 44.0, 42.7, 37.7, 35.0; IR (liquid film) 3449, 2927, 1771, 1715, 1275, 1110, 714 cm^{-1}; Mass (ESI, Pos., 20 V) *m*/*z* 459 (M + Na); Anal. Calcd for $C_{26}H_{28}O_6$: C, 71.54; H, 6.34; Found: C, 71.71; H, 6.34. HPLC conditions for the determination of diastereoselectivity: CHIRALCEL OD-RH; MeCN/H_2O = 30:70 (0−90 min); detection, 210 nm; flow rate, 1.0 mL/min; retention time of **2** was 63.4 min, and that of β-OH was 53.9 min. HPLC conditions for analysis of reaction: YMC-Pack-ODS-A-302; MeCN/H_2O = 45:55; detection, 210 nm; column temperature, 40 °C; flow rate, 1.0 mL/min; retention time of **2** was 9.2 min, and those of **1**, **3**, **4**, **5**, **6** were 13.6, 4.2, 6.4, 14.0, 10.2 min, respectively.

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