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Reconfirmation of High Enantiomeric Excesses in the Enantioselective Transformation of *meso*-Epoxides

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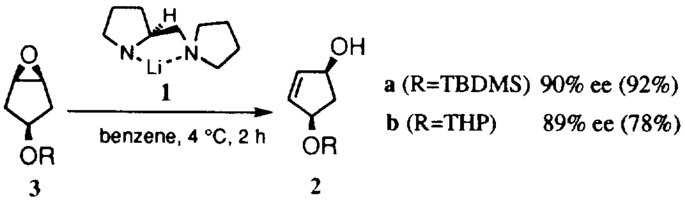
Abstract: Our previous results on the transformation of *meso*-epoxide 4-*t*-butyldimethylsiloxy-1,2-epoxycyclopentane by chiral lithium amide, lithium (*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidide, were fully reconfirmed to be highly enantioselective.

Asymmetric synthesis by the use of chiral lithium amides is emerging as a useful method for the preparation of non-racemic compounds.[1] We have been working on enantioselective transformation of *meso*-epoxides to allylic alcohol derivatives using lithium (*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidide (**1**)[2,3] as a part of our investigation on highly selective asymmetric reactions by the use of chiral diamine derived from (*S*)-proline.[4] The reaction was applied to highly enantioselective preparations of (1*S*,4*R*)-4-*t*-butyldimethylsiloxy-2-cyclopenten-1-ol (**2a**) and (1*S*,4*R*)-4-tetrahydropyranyloxy-2-cyclopenten-1-ol (**2b**), useful chiral building blocks for the synthesis of cyclopentanoid natural compounds, by the reaction of *meso*-epoxides, *cis*-4-*t*-butyldimethylsiloxy-1,2-epoxycyclopentane (**3a**) or *cis*-4-tetrahydropyranyloxy-1,2-epoxycyclopentane (**3b**) and **1** (Scheme 1).[3] Later a British group reported the same reaction in lower selectivity (76 %ee) in this journal.[5] It caused confusion about the selectivity of the reaction.[1b,6] Recently two other groups reported the same reaction using several chiral lithium amides[7,8] and described that they achieved the best results (up to 86 %ee and 88 %ee, respectively) for this type of transformation based on the British group's results. Here



Scheme 1

we wish to report our results of reinvestigation in order to clear up the confusion about the selectivities of the reaction of **3** with **1**.

In our initial study[3] we found an interesting solvent effect in the reaction of **3** with **1**. The selectivity of the reaction dramatically increased when the reaction was carried out in non-polar solvents. Higher selectivity was achieved in benzene (90 %ee) or hexane (88 %ee) than in THF (66 %ee) or ether (70 %ee). The British group reported that they could not observe such solvent effect (40 %ee in every case that THF, ether, and benzene was used as solvent) when they used a chiral diamine **4**, (*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidine, prepared by the reduction of (*S*)-1-prolylpyrrolidine, the conventional method we employed. However, they observed a similar solvent effect (THF 50 %ee; ether 60 %ee; benzene 76 %ee) when they used **4** prepared from (*S*)-prolinol (Table 1). They suggested possibility of partial racemization of the diamine during preparation by the conventional method to rationalize these results. However it is quite unusual that a different solvent effect was observed with the same reagent even if it was prepared by the different method and it can not be attributed to the racemization. Further, it is shown by the calculation from their results that the optical purity of the diamine **4** they obtained by the conventional method was 53–80 %ee. It is quite hard to consider such a large degree of racemization during the preparation because a number of highly selective (>80 %ee) asymmetric reactions were reported using diamine **4** and its derivatives prepared by the conventional method by others[1g,9] as well as our group.[4]

Table 1. Enantioselective Transformation of *meso*-Epoxide **3a** by Chiral Lithium Amide **1**.

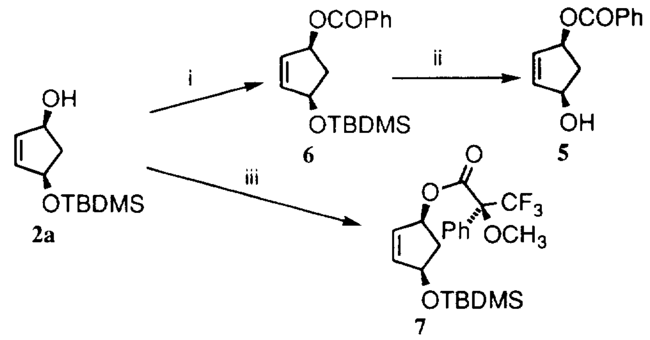
Solvent	Our result[3,a,c]	British group's results[5]	
		A[a]	B[b,c]
THF	66 %ee (76 %)	40 %ee	50 %ee (65 %)
ether	70 %ee (83 %)	40 %ee	60 %ee (58 %)
benzene	90 %ee (92 %)	40 %ee	76 %ee (73 %)
hexane	88 %ee (91 %)	—	—

[a] Diamine **4** prepared by the reduction of (*S*)-1-prolylpyrrolidine was used.

[b] Diamine **4** prepared from (*S*)-prolinol was used.

[c] Figures in parentheses are isolated yields.

They attributed the discrepancy of the ee's between our results and their results obtained by using **4** prepared from (*S*)-prolinol to a difference in methods of analysis. Namely, they described that we determined the ee's by specific rotation measurements of the compound with low rotation, which could be inaccurate. However, we had more than two evidences for the ee's of the products. Initially, the product **2a** ($[\alpha]_D^{22}$ +21.5 ° (*c* 0.94, $CHCl_3$)) was converted to (1*S*,4*R*)-4-hydroxy-2-cyclopentenyl benzoate **5** ($[\alpha]_D^{17}$ −120.2° (*c* 1.73, $CHCl_3$) as the specific rotation of chiral **2a** was not reported (Scheme 2). The ee of **5** was 90 % based on the reported value ($[\alpha]_D^{20}$ +133° (*c* 1.7, $CHCl_3$) for (1*R*,4*S*)-**5**).[10] Next, the same product was converted to (*R*)-4-acetoxy-2-cyclopentenone and the ee was confirmed to be more than 86 % on the basis of ^{1}H-NMR



Reagents and conditions: i benzoyl chloride, pyridine, 4-(dimethylamino)pyridine (DMAP) (catalytic amount), dichloromethane, room temperature, overnight; ii AcOH-THF-H_2O, room temperature, 14 h (Method A), or *n*-Bu_4NF, THF, room temperature, 2 h (Method B); iii (*S*)-MTPACl, DMAP (catalytic amount), pyridine, room temperature, overnight.

Scheme 2

taken with a chiral shift reagent, tris(heptafluorobutyryl-*d*-camphorato)europium (III), according to the reported method.[11] Furthermore several intermediates obtained during the course of derivation of (1*S*,4*R*)-**2a** to both (*R*)- and (*S*)-4-hydroxy-2-cyclopentenone all indicated that our product was around 90 %ee as described in the previous reports.[3] The specific rotation of **2a** reported recently by the Indian group[8] also supports high ee of our product.

Now we converted our product **2a** to Mosher's ester **7** to exclude any possibility that the difference of the ee's arose from the difference of the method (Scheme 2). The ee of **2a** was 90 %. We next examined HPLC analysis of the benzoate **5** using a chiral column (Waters Opti-pak TA) to make our results convincing. The ee of **5** was 89 %. Then we carried out the reactions in benzene by using the diamine **4** prepared from (*S*)-prolinol according to the British group's method and commercial one. As shown in Table 2 both diamines

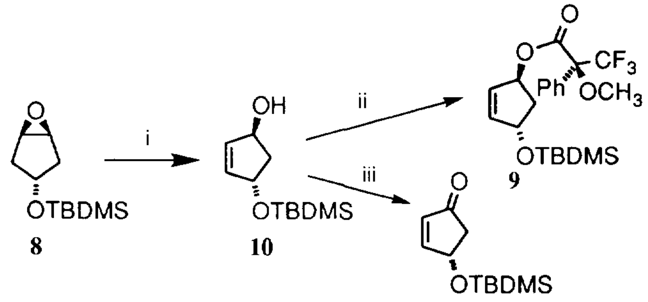
Table 2. Determination of ee of **2a**.

Run	Diamine **4**[a]	**2a**		De[c] of **7**/%	**5**	
		Yield[b]/%	$[\alpha]_D$(Temp, *c* ($CHCl_3$))		$[\alpha]_D$(Temp, *c* ($CHCl_3$))	Ee[d]/%
1	A	92	+21.5° (22 °C, 0.94)	90	−120.2° (17 °C, 1.73)	89 (90)
2	B	90	+20.3° (24 °C, 1.02)	86	−115.1° (25 °C, 1.74)	85 (87)
3	C	91	+21.1° (29 °C, 1.00)	88	−117.1° (28 °C, 1.82)	87 (88)

[a] A: Prepared by the reduction of (*S*)-1-prolylpyrrolidine[3b]; B: Prepared from (*S*)-prolinol[5]; C: Purchased from Aldrich Chemical Company, Inc., USA. [b] Isolated yield. [c] Diastereomeric excess (De) was determined by 500 MHz or 270 MHz ^{1}H-NMR. [d] Ee was determined by HPLC using a chiral column (Waters Opti-pak TA). Figures in parentheses are ee's based on the specific rotation.[10]

gave **2a** in high yields and ee's. Little discrepancy was observed due to the difference in methods of analysis. Thus the selectivity of the reaction of **3a** with **1** was proven to be high. The results obtained in other solvents shown in Table 1 were also confirmed to be 66 %ee (THF), 72 %ee (ether), and 90 %ee (hexane), respectively, by HPLC analyses of the benzoate **5**.

As there was also discrepancy in the level of ee between our results[3b] and the British group's results[6] for *trans*-4-*t*-butyldimethylsiloxy-1,2-epoxycyclopentane (**8**), we prepared the corresponding Mosher's ester **9** from (1*S*,4*S*)-4-*t*-butyldimethylsiloxy-2-cyclopenten-1-ol (**10**) ($[\alpha]_D^{20}$ −129.0° (*c* 0.69, CH_3OH)). The ee was confirmed to be 73 % which is in good accordance with the ee (74 %) determined by specific rotation after conversion to (*S*)-4-*t*-butyldimethylsiloxy-2-cyclopentenone (**11**) ($[\alpha]_D^{18}$ −50.2° (*c* 1.02, CH_3OH)) based on the reported value ($[\alpha]_D^{20}$ +67.4° (*c* 0.4, CH_3OH) for (*R*)-**11**)[12] (Scheme 3).



Reagents and conditions: i chiral lithium amide **1**, 1,8-diazabicyclo-[5.4.0]undec-7-ene, THF, room temperature, overnight; ii (*S*)-MTPACl, DMAP (catalytic amount), pyridine, room temperature, overnight; iii pyridinium chlorochromate, dichloromethane, room temperature, 2 h.

Scheme 3

In conclusion it was confirmed that high selectivity and high yield were achieved in the enantioselective deprotonation of **3a** by chiral lithium amide **1** without regard to the method for the preparation of the chiral diamine **4** or the method for the analysis of ee of **2a**. Therefore, this approach will become a useful method for the preparation of chiral cyclopentanoid natural products as already demonstrated by our group.[2e,f]

Experimental Section

^1H-NMR spectra were measured with Brucker AM500 spectrometer (500 MHz) or JEOL JNM-EX 270 (270 MHz) spectrometer, using tetramethylsilane as the internal standard. $CDCl_3$ was used as solvent. Specific rotation was measured on a Horiba SEPA-200. HPLC analyses were carried out with TOSOH instruments (pump, CCPS; detector, UV-8020).

Pyridine was distilled from KOH and then from CaH_2 and dried over MS 4A. The diamine **4** was prepared from (*S*)-1-prolylpyrrolidine[3b,13] or (*S*)-prolinol[6] (purchased from Tokyo Chemical Industry Co., Ltd.) according to the literature, and purchased from Aldrich Chemical Company, Inc., U. S. A., which was used after distillation ($[\alpha]_D^{25}$ +8.2° (*c* 2.47, C_2H_5OH)). The reactions of **3** and **8** with **1** were carried out by the same manner as described previously.[3b]

(1*S*,4*R*)-4-*t*-Butyldimethylsiloxy-2-cyclopentenyl Benzoate (6). Alcohol **2a** was treated with benzoyl chloride (2 eq.), pyridine (4 eq.), and a catalytic amount of 4-(dimethylamino)pyridine in dichloromethane in the same manner as described in the literature[3b] to afford **6** in 89–94 %. $[\alpha]_D^{29}$ –60.8° (*c* 1.83, hexane) in Run 1 in Table 2; $[\alpha]_D^{25}$ –59.3° (*c* 2.35, hexane) in Run 2 in Table 2; $[\alpha]_D^{28}$ –60.6° (*c* 2.42, hexane) in Run 3 in Table 2.

(1*S*,4*R*)-4-Hydroxy-2-cyclopentenyl Benzoate (5).

Method A: Benzoate **6** was stirred in AcOH-THF-H_2O (3:1:1) at room temperature for 14 h to afford **5** in 84% as described in the literature.[3b]

Method B: To a THF (2 ml) solution of **6** (124 mg, 0.39 mmol) was added a THF solution (1 ml of 1 M solution) of tetrabutylammonium fluoride at 0 °C under an argon atmosphere. After stirring for 1 h at room temperature, ether and saturated NH_4Cl solution were added to the reaction mixture. The organic layer was washed with water and brine, and dried over anhyd Na_2SO_4. The solvent was removed *in vacuo* and the residue was separated by preparative TLC (silica-gel, hexane/ether) to afford **5** (77 mg, 96 %) as white solid (mp 58–60 °C; lit,[10] 62–63 °C).

The specific rotations were shown in Table 2. The benzoate **5** was analyzed by HPLC using a chiral column (Waters Opti-pak TA (30 cm x 0.39 cm i.d.); 254 nm UV detector; eluent, 5% 2-propanol in hexane; flow rate, 0.5 ml/min; t_R, 25.8 min for minor peak, 28.8 min for major peak).

Preparation of 7, (*S*)-MTPA ester of 2a.[14] To a pyridine solution (1 ml) of the alcohol **2a** (15 mg) was added 7 drops of (*S*)-(–)-MTPA-Cl and a catalytic amount of 4-(dimethylamino)pyridine at room temperature. After the mixture was stirred overnight and the completion of the reaction was confirmed by TLC, the reaction was quenched with saturated NH_4Cl solution and the organic materials were extracted with ether. The organic phase was washed with saturated $CuSO_4$ solution to remove pyridine and brine and then dried over anhyd Na_2SO_4. After evaporation of the solvent crude MTPA ester **7** was obtained almost quantitatively as oil. This oil was analyzed by NMR. The follwing sets of the peaks were useful to determine ee. ^{1}H-NMR (500 MHz) δ=0.87 (s, major), 0.88 (s, minor); 1.66 (dt, *J* = 13.9, 4.9 Hz, major), 1.73 (dt, *J* = 13.9, 4.9 Hz, minor); 2.81 (dt, *J* = 14.1, 7.1 Hz, major), 2.86 (dt, *J* = 14.1, 7.1 Hz, minor); 5.87 (dt, *J* = 5.6, 1.6 Hz, minor), 5.96 (dt, *J* = 5.6, 1.6 Hz, major).

Preparation of 9, (*S*)-MTPA ester of 10.[14] Alcohol **10** ($[\alpha]_D^{20}$ –129.0° (*c* 0.69, CH_3OH)) was converted to the corresponding (*S*)-MTPA ester **9** in a similar manner as described for the preparation of **7**; The follwing sets of the peaks were useful to determine ee. ^{1}H-NMR (500 MHz) δ= 0.88 (s, major), 0.89 (s, minor); 2.18 (ddd, J = 14.6, 6.6, 2.1 Hz, major), 2.27 (ddd, J = 14.6, 6.6, 2.1 Hz, minor); 6.07 (dd, J = 5.4, 1.8 Hz, minor), 6.10 (dd, J = 5.4, 1.8 Hz, major).

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