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Optical Resolution of C_2-Symmetric Racemic 1,4-Diols with *o*-Xylylene Structure by Chiral Resolving Agent (*S*)-ALBO-V

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Optical resolution of C_2-symmetric racemic 1,4-diols, 1,2-bis(1-hydroxyalkyl)benzene, was examined using (*S*)-5-allyl-2-oxabicyclo[3.3.0]octene ((*S*)-ALBO-V) as chiral resolving agent. Diastereomeric acetals obtained from the 1,4-diols with (*S*)-ALBO-V were easily separated by silica-gel column chromatography. After removal of the resolving agent, both enantiomers of the 1,4-diols were obtained with high enantiomeric excesses.

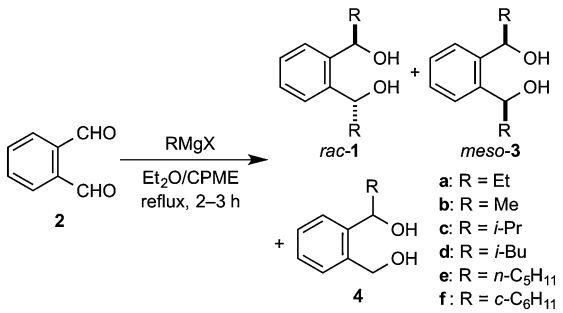
C_2-Symmetric 1,2-, 1,3-, and 1,4-diols have been recognized as useful chiral scaffolds in various asymmetric transformations as chiral ligands and chiral auxiliaries,[1–5] since the existence of a C_2-symmetric element is often important in asymmetric synthesis to induce high levels of stereoselectivity.[6] Among them, the structural variety of chiral C_2-symmetric 1,4-diols is rather limited, and the precise control of the stereochemical outcome of asymmetric reactions is generally difficult due to their structural flexibility except for 1,1′-bi-2-naphthol (BINOL) derivatives[3] and α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) derivatives[4] with relatively rigid structures.

We have reported the asymmetric synthesis of chiral C_2-symmetric 1,4-diols with *o*-xylylene structure, (*S*,*S*)-1,2-bis(1-hydroxyalkyl)benzene (**1**), and the use of (*S*,*S*)-1,2-bis(1-hydroxypropyl)benzene (**1a**) (R = Et) as chiral auxiliary or starting material of chiral ligands.[7] The superiority of chiral 1,4-diol **1a** as chiral auxiliary was shown in the 1,4-addition of phenyllithium to a β-nitrostyrene derivative by comparing the results using other C_2-symmetric chiral 1,2-, 1,3-, and 1,4-diols.[7c] In the previous report,[7a] however, the stepwise enantioselective addition of dialkylzinc reagent to aromatic aldehyde was utilized for the construction of two benzylic stereogenic centers of 1,4-diol **1**. Therefore, the examples of chiral 1,4-diols **1** with high enantiomeric excesses have been limited to **1a** and **1b** (R = Me). Although van Koten et al. also reported the enantioselective synthesis of several examples of 1,4-diol **1**, the enantioselectivities of the reactions were less than 90%.[8]

On the other hand, optical resolution is another method to obtain optically active compounds. As for the optical resolution of chiral secondary alcohols, (*S*)-5-allyl-2-oxabicyclo[3.3.0]-octene ((*S*)-ALBO-V) was reported as a useful chiral resolving agent.[9] Various diastereomeric acetals prepared from racemic secondary alcohols with (*S*)-ALBO-V were easily separated by silica-gel column chromatography, and both enantiomers of the alcohols with high enantiomeric excesses were easily obtained after removal of (*S*)-ALBO-V by deacetalization. Herein, we established a facile procedure for the preparation of both enantiomers of chiral 1,4-diols **1** bearing various alkyl groups by optical resolution using (*S*)-ALBO-V.

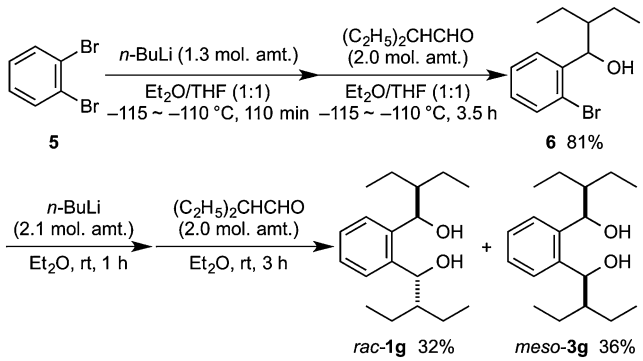
In the first place, various racemic 1,4-diols **1a**–**1g** were synthesized from *o*-phthalaldehyde (**2**) and the corresponding Grignard reagents according to a known procedure with slight modification (Table 1).[10] Namely, to dialdehyde **2** in cyclopentyl methyl ether (CPME) was added an ethereal solution of ethylmagnesium bromide, prepared from 2.5 molar amounts of bromoethane, at 0 °C and the reaction mixture was refluxed for 3 h. After acidic work-up, a mixture of desired 1,4-diol *rac*-**1a**, its diastereomer *meso*-**3a**, and reduced product **4a**, which resulted from a single nucleophilic addition followed by a reduction by β-hydrogen of the Grignard reagent, were obtained in 55%, 13%, and 16% yields, respectively (Entry 1). Similarly, the reaction with methylmagnesium iodide gave *rac*-**1b** and *meso*-**3b** in 46% and 47% yields, respectively (Entry 2). As for the synthesis of *rac*-**1c**, the amount of isopropylmagnesium bromide was increased to that prepared from 5.0 molar amounts of 2-bromopropane until **2** was not detected by TLC, and *rac*-**1c** was obtained in 29% yield along with *meso*-**3c** and **4c** with 6% and 31% yields, respectively (Entry 3). 1,4-Diols **1d**–**1f** were also obtained in 37–57% yields by the reaction of **2** with Grignard reagents prepared from 4–5 molar amounts of the corresponding alkyl halides (Entries 4–6).

Table 1. Synthesis of Racemic 1,4-Diols **1a**–**1f**



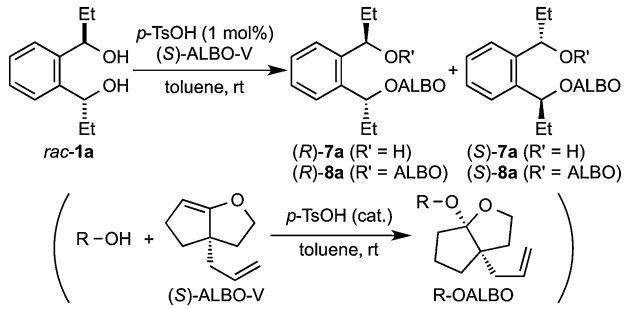
Entry	RMgX[a)]	*rac*-**1** /%[b)]	*meso*-**3** /%[b)]	**4** /%[b)]
1	EtMgBr (2.5)	55	13	16
2	MeMgI (2.5)	46	47	0
3	*i*-PrMgBr (5.0)	29	6	31
4[c)]	*i*-BuMgBr (4.0)	37	15	39
5	n-C_5H_{11}MgBr (5.0)	41	23	34
6	c-C_6H_{11}MgCl (5.0)	57	14	14

a) Molar amounts of the corresponding alkyl halides used were in parentheses. b) Isolated yield. c) The reaction was carried out at room temperature.



Scheme 1. Synthesis of 1,2-bis(2-ethyl-1-hydroxybutyl)-benzene (**1g**).

Table 2. Acetalization of *rac*-**1a** with (*S*)-ALBO-V



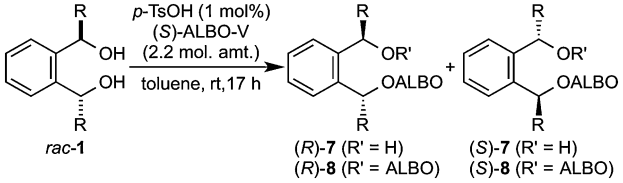
Entry	(*S*)-ALBO-V /mol. amt.	Time /h	**7a**/%[a]		**8a**/%[a]	
			(*R*)	(*S*)	(*R*)	(*S*)
1[b]	1.0	3	22	26	6	9
2	2.0	10	15	8	29	41
3	3.0	7	Trace	Trace	42	45
4	2.2	17	9	4	40	45

a) Isolated yield. b) Recovery of *rac*-**1a** was 13%.

1,2-Bis(2-ethyl-1-hydroxybutyl)benzene **1g** was prepared from 1,2-dibromobenzene (**5**), since the reaction of 1-ethylpropylmagnesium halide with **2** afforded *rac*-**1h** in ca. 10% yield due to the predominant formation of **4g** and 1,2-bis(hydroxymethyl)benzene. Dibromide **5** was mono-lithiated by butyllithium in Et_2O/THF at between −115 and −110 °C, and the resulting aryl lithium was reacted with 2-ethylbutanal to give bromoalcohol **6** in 81% yield. Treatment of **6** with butyllithium in Et_2O at room temperature, and the subsequent reaction with 2-ethylbutanal afforded *rac*-**1g** and *meso*-**3g** in 32% and 36% yields, respectively (Scheme 1).

Next, the optical resolution of *rac*-**1a** was examined using (*S*)-ALBO-V (Table 2). When *rac*-**1a** was mixed with 1.0 molar amount of (*S*)-ALBO-V in the presence of a catalytic amount (1 mol %) of *p*-toluenesulfonic acid in toluene at room temperature for 3 h, diastereomers of monoacetals (*R*)-**7a** and (*S*)-**7a** were obtained in moderate yields along with diastereomeric diacetals (*R*)-**8a** and (*S*)-**8a**. The resulting four products ((*R*)-**7a**, (*S*)-**7a**, (*R*)-**8a**, and (*S*)-**8a**) were separated by a single silica-gel column chromatography (Entry 1). The reaction was then examined using 2.0 molar amounts of (*S*)-ALBO-V, and diacetals (*R*)-**8a** and (*S*)-**8a** were obtained in 29% and 41% yields, respectively (Entry 2). Monoacetals were fully converted to diacetals by using 3.0 molar amounts of (*S*)-ALBO-V,

Table 3. Acetalization of Various 1,4-Diols with (*S*)-ALBO-V



Entry	**1**	R	**7**/%[a]		**8**/%[a]	
			(*R*)	(*S*)	(*R*)	(*S*)
1	**1b**	Me	Trace	Trace	40	43
2	**1c**	*i*-Pr	15	5	28	42
3	**1d**	*i*-Bu	5	Trace	45	46
4[b]	**1e**	n-C_5H_{11}	7	Trace	37	42
5	**1f**	c-C_6H_{11}	14	5	30	37
6[c]	**1g**	$(C_2H_5)_2CH$	14	6	28	39

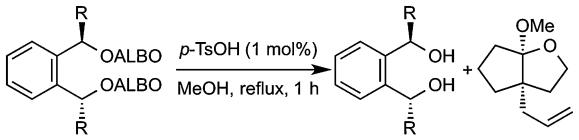
a) Isolated yield. b) Reaction time was 3 h. c) Reaction was carried out using 20 mol % of *p*-TsOH.

and (*R*)-**8a** and (*S*)-**8a** were obtained in high isolated yields (Entry 3). The amount of (*S*)-ALBO-V was reduced to 2.2 molar amounts to give (*R*)-**8a** and (*S*)-**8a** in 40% and 45% yields, respectively (Entry 4).

As a good result was obtained for *rac*-**1a**, the optical resolution of various 1,4-diols **1b**–**1g** was then examined (Table 3). When **1b** (R = Me), **1d** (R = *i*-Bu), and **1e** (R = n-C_5H_{11}) were reacted with (*S*)-ALBO-V, diacetals **8b**, **8d**, and **8e** were obtained in high isolated yields (Entries 1, 3, and 4). In the cases of **1c** (R = *i*-Pr) and **1f** (R = c-C_6H_{11}), diacetals (*S*)-**8c** and (*S*)-**8f** were obtained in high yields although ca. 15% of monoacetals (*R*)-**7c** and (*R*)-**7f** were isolated and the yields of (*R*)-**8c** and (*R*)-**8f** were moderate probably due to the steric hindrance of the substituents (Entries 2 and 5). The yields of (*R*)-**8c** and (*R*)-**8f** were not improved by elongation of the reaction time or increasing the amount of *p*-toluenesulfonic acid. As for 1,4-diol **1g** (R = $(C_2H_5)_2CH$), a higher catalyst loading (20 mol %) was required for the formation of diacetals (*R*)-**8g** and (*S*)-**8g** (28% and 39% yields, Entry 6). All diastereomeric diacetals (*R*)-**8b**–**8g** and (*S*)-**8b**–**8g** were also separated by silica-gel column chromatography.

As both enantiomers of various 1,4-diols **1a**–**1g** were obtained in diacetal form with (*S*)-ALBO-V, deacetalization of diacetals **8a**–**8g** was carried out to obtain (*R*)-**1a**–**1g** and (*S*)-**1a**–**1g** (Table 4). In the presence of 1 mol % of *p*-toluenesulfonic acid, a methanol solution of diacetal (*R*)-**8a** was heated under reflux for 1 h to give (*R*)-**1a** in 98% yield with 98% ee (Entry 1). The chiral resolving agent was recovered as methanol adduct, which is the precursor of (*S*)-ALBO-V and therefore reusable.[9] Similarly, deacetalization of (*S*)-**8a** afforded (*S*)-**1a** in 96% yield with 97% ee (Entry 2). Deacetalization of other diacetals, (*R*)-**8b**–**8g** and (*S*)-**8a**–**8g**, also proceeded to give the corresponding 1,4-diols (*R*)-**1b**–**1g** and (*S*)-**1a**–**1g** in high yields and enantiomeric excesses (Entries 3–14). Although the ee values of 1,4-diols **1a**–**1g** should be >99% in principle since enantiomerically pure (*S*)-ALBO-V was used as chiral resolving agent, the ee values were 92–98% in some cases. This is probably due to the technical problem in the separation of diastereomeric diacetals (*R*)-**8** and (*S*)-**8** by silica-gel column

Table 4. Deacetalization of Various Acetals **8**



(*R*)-**8** or (*S*)-**8** (*R*)-**1** or (*S*)-**1**

Entry	R	Acetal	Yield/%[a)]	ee/%[b)]
1	Et	(*R*)-**8a**	98	98
2		(*S*)-**8a**	96	97
3	Me	(*R*)-**8b**	95	98
4		(*S*)-**8b**	96	98
5	*i*-Pr	(*R*)-**8c**	86	97
6		(*S*)-**8c**	87	99
7	*i*-Bu	(*R*)-**8d**	72	92 (>99)[c)]
8		(*S*)-**8d**	79	98 (>99)[c)]
9	n-C_5H_{11}	(*R*)-**8e**	85	96
10		(*S*)-**8e**	88	>99
11	c-C_6H_{11}	(*R*)-**8f**	92	>99
12		(*S*)-**8f**	81	98
13	$(C_2H_5)_2CH$	(*R*)-**8g**	84	97
14		(*S*)-**8g**	85	96

a) Isolated yield. b) Determined by HPLC analysis. c) After single recrystallization.

chromatography. In the case of **1d**, enantiomerically pure samples (>99% ee) were obtained for both enantiomers after single recrystallization from Et_2O/hexane.

In conclusion, various C_2-symmetric *rac*-1,4-diols with *o*-xylylene structure were synthesized from the easily available starting materials in one or two steps with good yields. Acetal-type chiral resolving agent (*S*)-ALBO-V was found to be useful for the optical resolution of 1,4-diols **1**, and both enantiomers of **1** were obtained with high enantiomeric excesses. The chiral 1,4-diols obtained in this study would find applications in various kinds of asymmetric transformations as chiral ligands or chiral auxiliaries.

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Supporting Information

Details of experimental procedures and characterization data of synthesized compounds. This material is available electronically on J-STAGE.

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