An Efficient Enantioselective Preparation of (*S*,*S*)-1,2-Bis(1-hydroxyalkyl)benzene

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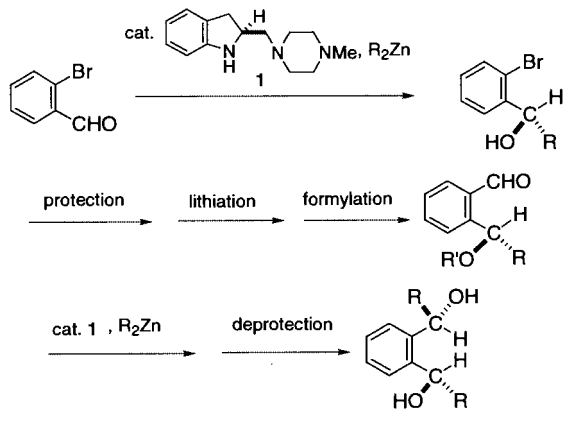
(S,S)-1,2-Bis(1-hydroxyalkyl)benzenes were obtained in >99% ee's with high diastereoselectivity by the enantioselective addition of dialkylzinc to (*S*)-2-[1-(4-methoxybenzyloxy)alkyl]-benzaldehyde (86% ee) in the presence of a catalytic amount of (*S*)-2-(4-methylpiperazin-1-ylmethyl)indoline.

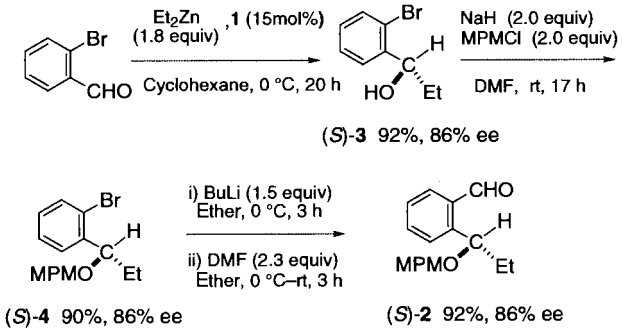
C_2-Symmetric chiral 1,2-, 1,3-, and 1,4-diols are useful reagents in asymmetric synthesis[1] as chiral auxiliaries, chiral ligands, and starting materials for various chiral compounds having other functionalities.[2] Asymmetric dihydroxylation of olefins[3] and asymmetric reduction of diketones are successfully employed for the preparation of this class of compounds.[4] Enantioselective alkylation of dialdehyde was also examined using *B*-allyldiisopinocamphenylborane[5] or dialkylzinc in the presence of a chiral catalyst.[6,7] However, (*R*,*R*)-1,2-bis(1-hydroxypropyl)benzene of 92% ee was obtained only as a minor product (*dl*/*meso* = 9/91) in the catalytic diethylation of phthalaldehyde.[7b] With regard to the asymmetric reduction of 1,2-diacylbenzenes to produce chiral 1,2-bis(1-hydroxyalkyl)-benzene, catalytic oxazaborolidine-BH_3 reduction gave chiral 1,2-bis(1-hydroxyethyl)benzene in 90% ee (48%)[8] while *B*-chlorodiisopinocamphenylborane gave unsuccessful result.[9] These results prompted us to develop an efficient method to prepare chiral 1,2-bis(1-hydroxyalkyl)benzene in high ee and examine its use in asymmetric synthesis. In this communication we wish to report an efficient method for the preparation of *(S,S)*-1,2-bis(1-hydroxyalkyl)benzene starting from 2-bromobenzaldehyde by dual enantioselective addition of dialkylzinc to aldehyde using (*S*)-2-(4-methylpiperazin-1-yl)methylindoline (**1**)[10] as catalyst.

First we examined reactions of excess diethylzinc with phthalaldehyde or 2-(1-hydroxypropyl)benzaldehyde (1-hydroxy-3-ethyl-2-oxaindane) in cyclohexane at room temperature using 40 mol% or 10 mol% **1**, respectively. As the starting materials were recovered in both reactions, we focused our efforts on the reaction of 2-(1-alkoxyalkyl)benzaldehyde (Scheme 1).



Scheme 1.

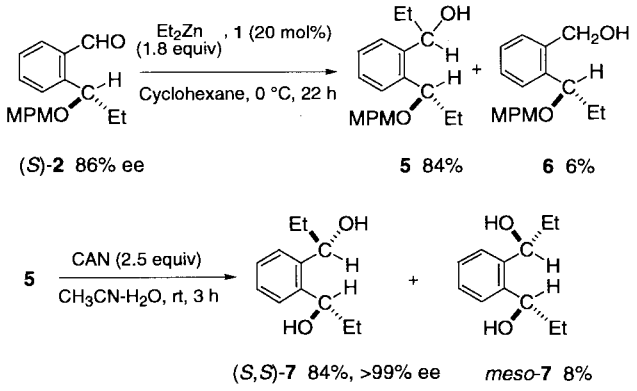
(*S*)-2-[1-(4-methoxybenzyloxy)propyl]benzaldehyde, (*S*)-**2** was employed as 2-(1-alkoxyalkyl)benzaldehyde since 4-methoxybenzyl group was removed selectively in the presence of benzylic hydroxyl group under mild reaction conditions. In the first place 2-bromobenzaldehyde was converted to (*S*)-1-(2-bromophenyl)propanol, (*S*)-**3**[11] (86% ee, $[\alpha]_D^{20}$ –40.4° (*c* 1.32, $CHCl_3$)) in 92% yield by catalytic enantioselective addition of diethylzinc using 15 mol% **1**. After treatment of (*S*)-**3** with 4-methoxybenzyl chloride (MPMCl), ((*S*)-**4**,[12] 90%, $[\alpha]_D^{20}$ –42.1° (*c* 1.02, $CHCl_3$)), (*S*)-2-(1-(4-methoxybenzyloxy)propyl)-benzaldehyde, (*S*)-**2**[12] ($[\alpha]_D^{20}$ –92.4° (*c* 1.00, $CHCl_3$)) was obtained in 92% yield by lithiation of (*S*)-**4** with butyllithium followed by the reaction with DMF (Scheme 2).



Scheme 2.

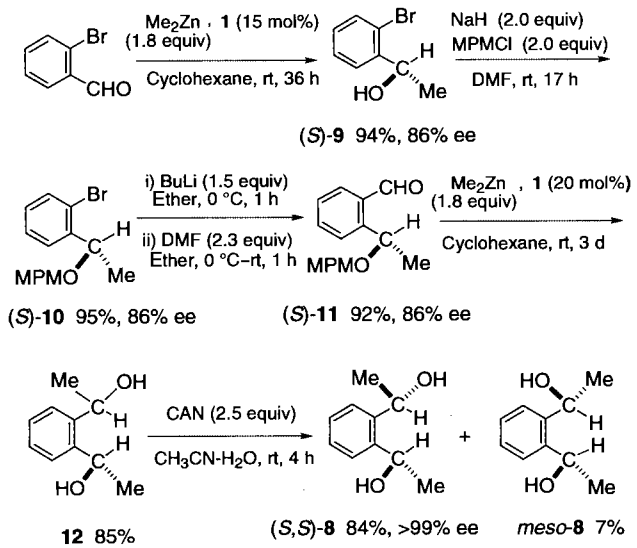
Enantioselective ethylation of (*S*)-**2** was then examined using 1.8 equiv diethylzinc in the presence of 20 mol% **1** in cyclohexane. A mixture of stereoisomers of 1-[2-{1-(4-methoxybenzyloxy)propyl}]phenylpropanol (**5**)[12] was obtained in 84% yield along with 1-[2-{1-(4-methoxybenzyloxy)-propyl}]benzyl alcohol, **6**[12] (6% yield). Removal of the protecting group of **5** with cerium ammonium nitrite (CAN) in CH_3CN/H_2O (9/1)[13] afforded (*S*,*S*)-**7**[14] (84%, >99% ee, $[\alpha]_D^{20}$ –55.4° (*c* 0.87, $CHCl_3$)) and *meso*-**7**[7b] (8%) (*dl*/*meso* = 91/9) (Scheme 3).

We assume that the second addition reaction is irrelevant to the other chiral center formed in the first addition reaction and the enantioselectivity of the second addition reaction is high for both (*S*)- and (*R*)-**2**. Thus (*S*)-**2**, the major enantiomer in the first addition reaction, afforded exclusively (*S*,*S*)-**5** with a small amount of *meso*-type **5**. On the other hand, most of (*R*)-**2**, the minor enantiomer in the first addition reaction, was converted to *meso*-type **5** and little (*R*,*R*)-**5** was formed. Consequently, (*S*,*S*)-**7** was obtained in high (>99%) ee with a small amount of easy separable *meso*-**7** after removal of protecting group.



Scheme 3.

Next enantio- and diastereoselective synthesis of *(S,S)*-1,2-bis(1-hydroxyethyl)benzene, (*S*,*S*)-**8**, was examined by a similar reaction sequence. (*S*)-2-[1-(4-Methoxybenzyloxy)ethyl]-benzaldehyde, (*S*)-**11**[12,15] (86% ee, $[\alpha]_D^{20}$ –83.1° (*c* 1.02, $CHCl_3$)) was obtained from 2-bromobenzaldehyde in three steps in 82% yield. The second addition reaction afforded a mixture of stereoisomers of 1-[2-{1-(4-methoxybenzyloxy)-ethyl}]phenylethanol, **12**[12] in 85% yield, and *S*,*S*-**8**[8,16] ($[\alpha]_D^{20}$ –72.4° (*c* 1.00, $CHCl_3$)) was obtained in 84% yield in high (>99%) ee along with *meso*-**8**[17] (7% yield) (*dl*/*meso* = 92/8) after deprotection with CAN (Scheme 4).



Scheme 4.

It should be noted that an efficient enantio- and diastereoselective synthesis of chiral 1,4-diols, (*S*,*S*)-1,2-bis(1-hydroxypropyl)benzene, (*S*,*S*)-**7**, and (*S*,*S*)-**8**, were achieved using catalytic dual enantioselective addition of dialkylzinc to aldehydes, starting from 2-bromobenzaldehyde. As the usefulness of (*S*,*S*)-**7** was realized in an asymmetric photochromic cyclization,[18] further applications of the chiral 1,4-diols in asymmetric synthesis is now in progress.

References and Notes

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11 The ee value was determined by HPLC using Daicel Chiralcel OB and the absolute configuration was assigned to be *S* as (*S*,*S*)-**7** was obtained afterwards.

12 Satisfactory spectral data (^{1}H NMR, ^{13}C NMR, IR) were obtained for these compounds.

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14 The ee value was estimated to be >99% as only one enantiomer was detected by HPLC using Daicel Chiralcel OD-H. The absolute configuration was established by comparison of the specific rotation with reported value.[7b]

15 The ee value of (*S*)-**9** ($[\alpha]_D^{20}$ –47.8° (*c* 1.00, $CHCl_3$)) was determined to be 86% by HPLC using Daicel Chiralcel OB and the absolute configuration of (*S*)-**9** was established by comparison of the specific rotation with reported value; S. Sato, H. Watanabe, and M. Asami, *Tetrahedron: Asymmetry*, **11**, 4329 (2000).

16 The ee value was estimated to be >99% as only one enantiomer was detected by HPLC using Daicel Chiralcel OD-H. The absolute configuration was assigned to be *S*,*S* as the chiral center created in the first reaction was *S*.

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