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Enantioselective Synthesis of C_2-Symmetric Diols

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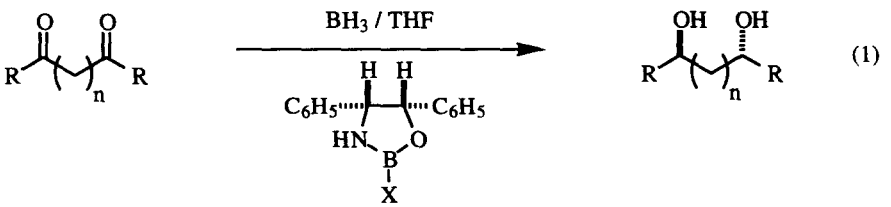
ABSTRACT: *Catalytic reduction of diketones with erythro diphenyl oxazaborolidine yielded C_2-symmetric diols in high enantiomeric excess. Enantiomeric excess increased and less meso isomer was generated when borane was employed equimolar with respect to the carbonyl groups and when stoichiometric oxazaborolidine was used.*

The importance of diols containing a C_2 axis of symmetry in asymmetric synthesis continues to grow. Catalysts employed in asymmetric epoxidation[1] and enantioselective organometallic addition to aldehydes[2] are prepared from the 1,2-diol in tartaric acid. Asymmetric dihydroxylation of olefins[3] is one of the newer preparative methods of 1,2-diols and complementary to this is the resolution with Dispoke (dispiroketal).[4] Asymmetric alkylation,[5] aldol,[6] free radical addition,[7] and hydrogenation[8] reagents are derived from 1,4-diols. Enzymatic esterification of meso racemate mixtures[9] and Kolbe coupling of β-hydroxy acids are the current routes to these 1,4-diols.[10] A general method to synthesize a number of C_2-symmetric diols in an enantioselective manner was initiated to support our synthetic studies due to limitations of the present methods. Oxazaborolidine reduction of diketones was evaluated as an expedient route to these diols.

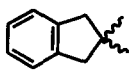
Diketones were first reduced with borane to provide authentic samples of the meso and racemic diols, Table. The borane reductions had an inherent preference for the meso isomer ranging from 1:1 to 5:1 (meso : racemate). A variety of achiral hydride reagents were previously observed to form predominately the meso isomer in reduction of benzil.[11] *In situ* formed B-H[12] and isolated B-Me erythro diphenyl oxazaborolidines[13] were then evaluated for the enantioselective preparation of diols, equation 1.[14]



(1)

Oxazaborolidine catalyzed reductions managed to override the meso isomer preference observed in the uncatalyzed borane reductions. Benzil reduction, entries 2-4, provided an 85%ee with a 1:1 meso to R,R ratio.[15] The benzoyl group was sterically more demanding than the phenyl group in the reduction of benzil

Table[16]

Entry	Diketone #; R; n	Oxazaborolidine X / mole %	Meso / R,R+S,S	%ee (R,R or S,S)
1	**1**; R = C_6H_5; n=O	none	83 / 17	
2		H / 5	59 / 41	86 (R,R)
3		H / 10	48 / 52	85 (R,R)
4		Me / 10	61 / 39	70 (R,R)
5	**2**[a,b]; R = Me; n =	none	85 / 15	
6		Me / 10	36 / 64	92 (S,S)
7	**3**; R = Me; n = 2	none	43 / 57	
8		H / 10	31 / 69	17 (S,S)
9	**4**; R = C_6H_5; n = 2	none	61 / 39	
10		H / 10	21 / 79	94 (S,S)
11		H / 100	16 / 84	99 (S,S)
12		H / 100	16 / 84	99 (S,S)[d]
13	**5**[c,e]; R = t-Bu; n = 2	none	67 / 33	
14		H / 10	20 / 80	97 (S,S)
15	**6**[e]; R = C_6H_5; n = 3	none	57 / 43	
16		H / 10	14 / 86	99 (S,S)
17		H / 10	9 / 91	99 (S,S)[d]
18		H / 100	2 / 98	99 (S,S)
19		Me / 10	16 / 84	96 (S,S)
20	**7**[e]; R = C_6H_5; n = 4	none	50 / 50	
21		H / 10	12 / 88	94 (S,S)
22		Me / 10	11 / 89	99 (S,S)[d]

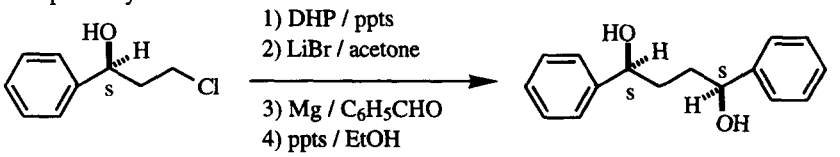
a) Prepared from α,α'-dichloro-o-xylene, 2,4-pentanedione, potassium carbonate. b) Absolute stereochemistry assigned based on analogy see reference 17. c) Prepared by the method of Saegusa, J. Am. Chem. Soc. 1975, 2912. d) Two equivalents of borane methyl sulfide complex per diketone were employed. e) Absolute stereochemistry assigned on analogy to entry 10.

which may result from aligning the C=O groups anti to one another, thereby minimizing the carbonyl dipole-dipole interactions. When two, three, or four methylene groups were present between the benzoyl substituents, diols were formed in high enantiomeric excess with less meso isomer (entries 10, 16, 21). Low enantiomeric excess with 2,5-hexanedione was the result of similar steric demands of the groups flanking the carbonyl group. In this case, the methylene groups dominated over the methyl group as demonstrated previously in the reduction of 2-hexanone.[17] The t-butyl group in the 1,4-diketone, entry 14, yielded 97% enantiomeric excess. In catalyzed reductions, the meso isomer resulted when hydride addition opposite to the catalyzed path occurred for one of the two diketone carbonyl groups.

Additives,[18] stoichiometric oxazaborolidine, and stoichiometric use of borane[19] (relative to the carbonyl group) have provided higher ee in reductions with the CBS catalyst.[20] Less meso isomer was generated when one equivalent of borane (in place of the typical 0.7 equivalents) per carbonyl group was used, entries 17 and 22.[21] Thus, uncatalyzed borane reduction of the diketone was not responsible for all the meso isomer. Optimization of dibenzoylpropane reduction with stoichiometric oxazaborolidine, entry 18, led to only 2% of the meso isomer. Crystallization of this product yielded the 1,5-diol with <1% meso isomer in 99%ee.

The spiro diketone, entry 6, gave 92%ee and significant amount of the meso isomer. Of all the diketones reduced, this one gave a borane complex which required refluxing methanol to obtain the diol. Intramolecular delivery of hydride to this spirodiketone may be responsible for the high meso content.

Absolute stereochemistry of the diols produced from benzil **1**[15] and 2,5-hexanedione **3**[9] were known as a result of literature precedent, and the diol derived from spirodiketone **2** was based on similarity to the prior art.[17] The remaining 1,4-, 1,5-, and 1,6-diols absolute stereochemistry was assigned on analogy to the dibenzoylethane case, entry 10, was determined as follows. 1(S)-Phenyl-(3)-chloropropanol has been synthesized by a number of enantioselective hydride[22] and enzymatic reductions.[23] Dihydropyran protection of the hydroxyl group and subsequent halogen exchange with lithium bromide in acetone afforded the diastereomeric bromides, equation 2. The Grignard reagent was formed in ether and reacted with benzaldehyde. Pyridinium tosylate removal of the THP protecting group provided a 41:59 ratio of two products. Since the starting (S)-alcohol was employed, the products were assigned as (S,S)[24] and the meso diol respectively.



+ Meso (2)

41 : 59

In summary, the inherent preference for the meso isomer formation using borane as a reductant was overridden by use of oxazaborolidines. Employing an equimolar quantity of borane with respect to the carbonyl groups and/or stoichiometric oxazaborolidine increased enantiomeric excess and lowered the meso isomer level. Crystallization was demonstrated to afford high ee and isomeric purity. Enantioselective reduction of diketones provides an expedient route to C_2-symmetric diols.

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15. (R,R)-1,2-diphenyl-1,2-ethane diol has been prepared by asymmetric dihydroxylation. Wang, Z-M.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 8302-3.
16. All reductions were performed on 10 mmole scale with 1.4 equivalents of borane unless noted otherwise. Representative *in situ* reduction conditions exemplified for entry 10 are as follows: (1S,2R)-2-amino-1,2-diphenylethanol (213mg, 1mmol) was dissolved in tetrahydrofuran (40mL) under a nitrogen atmosphere. Borane dimethylsulfide complex (2M in THF, 7mL) was added in one portion and the contents stirred for 18hrs. Dibenzoyl ethane (2.38g, 10mmol) in tetrahydrofuran (15mL) was added dropwise over 1hr, the reaction strirred for 1hr, and cautiously quenched at 0°C with methanol (27mL). Workup provided the diol αD= -10.2 (c=1, MeOH), 94%ee. Enantiopurity of the diols was determined as follows (diol rotations): **1** Chiralpak AD 10% IPO/hexane (Lit. reference 15); **2** Chiralcel OG 5% IPO/hexane (entry 6, αD= -17.5 (c=1, MeOH)); **3** %ee by rotation, % meso by ^{13}C (Lit. reference 9a); **4** Chiralpak AD 20% isopropanol/hexane (Lit. reference 24); **5** Cyclobond I, SN with the 1-naphthylisocyanate derivative (entry 14, αD= -34.3 (c=1, MeOH)); **6** (R,R) Whelk-01 5% IPO/hexane (entry 18, αD= -22.8 (c=1, MeOH)); **7** Chiralpak AS 10% IPO/hexane (entry 22, αD= -12.6 (c=1, MeOH)).
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