Stereoselective Reduction of Benzils: A New Convenient Route to Enantiomerically Pure 1,2-Diarylethanediols

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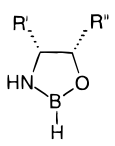
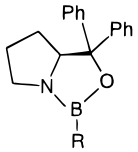
In recent years there has been an emphasis placed on C_2-symmetric auxiliaries during the design of enantioselective catalysts.[1] Among various C_2-symmetric diols, hydrobenzoin and its derivatives have received particular attention owing to their diverse applications.[2] Although several enantioselective routes to the parent compound itself are available, including the most useful asymmetric dihydroxylation (ADH), there is no general procedure for the synthesis of 1,2-diarylethanediols. We present here our results dealing with the stereoselective reduction of benzils providing a convenient preparation of the corresponding enantiomerically pure diols.

Oxazaborolidine-catalyzed reduction of prochiral ketones has been one of the most studied reaction during the past decade.[3] In spite of the numerous reports, reduction of functionalized ketones and the problem of diastereoselectivity have been scantily addressed. Our interest in the synthesis of certain C_2-symmetric diols prompted us to examine precisely these aspects. The reduction of benzil under various conditions is known to provide predominantly the *erythro* diastereomer.[4] Our attempts to modify the reagent or the reaction conditions did not significantly alter the diastereoselectivity. We were surprised to discover that oxazaborolidine-catalyzed reduction with borane−methyl sulfide complex (BMS) provided a higher ratio of *threo/erythro* diols. Equally intriguing was the fact that the diastereoselectivity was dependent upon the structure of the catalyst employed.

Four structurally diverse oxazaborolidines **(1a, 1b, 2a,** and **2b)** were selected as representative catalysts. A



1a R' = Me, R" = Ph
1b R' = R" = Ph



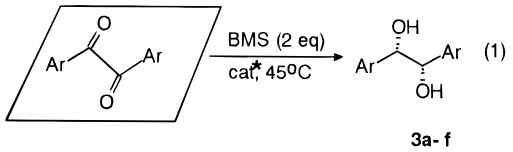
2a R = Me
2b R = H

solution of the catalyst (10 mol %) and BMS (2 equiv) in toluene was treated with a solution of dione (1 equiv) while the temperature was maintained at 45 °C. The addition rate was adjusted in such a way that the continuous disappearance of yellow color acted as the monitor for the progress of the reaction (eq 1). The diastereomeric composition of the product was analyzed by ^{1}H NMR. In some cases **(3b, 3e,** and **3f)** better separation for the benzylic protons was obtained with the corresponding diacetates. Salient observations as a function the catalyst structure and the reaction conditions were as follows: (1) an *in situ* prepared catalyst is as efficient as the conventionally preformed one, (2) optimum reaction temperature, the most critical parameter for the reduction is in the range of 45 °C, (3) at the specified temperature, the solvent and the substituent on the B atom do not significantly influence either the rate or the diastereoselectivity of the reduction. Some, though not all, of these observations are in agreement with the reported ones. By all considerations, **2b** proved to be the most efficient and reliable catalyst, providing an 88:12 ratio of *threo/erythro* diastereomers[5] (Table 1).

Table 1. Reduction of Benzil to Hydrobenzoin

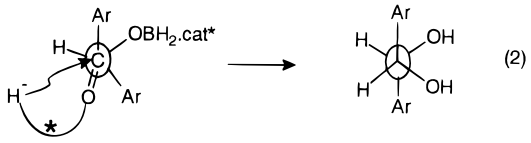
reagent	solvent	catalyst	temp, °C	time, min	*threo: erythro*[a]
$NaBH_4$	MeOH		25	120	0:100
LAH	THF		0	30	4:96
$LiAl(O^tBu)_3H$	THF		0	120	20:80
BMS	THF		25	*b*	
BMS	THF	**1a**	25	180	27:73
BMS	THF	**1b**	25	60	42:58[c]
BMS	THF/toluene	**2a**	25	120	66:34
BMS	THF/toluene	**2a**	45	15	87:13
BMS	THF/toluene	**2b**	45	<5	88:12

[a] Determined by ^{1}H NMR. [b] No appreciable reaction after 24 h. [c] Reference 8.



3a- f

As for the mechanism, we believe that the reduction of benzil involves fast and consecutive attack on both the keto groups placed in antiperiplanar conformation. The chiral reagent first attacks almost exclusively the *re* face of one of the carbonyl groups to produce the *S* configuration at the stereogenic center. This is then followed by diastereoselective reduction of the second carbonyl group (eq 2).



The realization of very high enantioselectivity was not surprising considering the fact that all the catalysts selected in the present study are known to provide >90% ee for the reduction of acetophenone.[6] We were, however, puzzled by the origin of the *erythro* isomer and its dependence on the catalyst structure. It is possible that either the intermolecular reduction of the second carbonyl group is not stereospecific or the reduction takes place *via* an intramolecular process involving the initially formed OBH_2 group. A convincing answer was provided by the reduction of chiral benzoin. Treatment of *(S)*-benzoin with 2 equiv of BMS in the presence of 10 mol % **2b** or with 1 equiv of BMS in the absence of the catalyst both produce exclusively *erythro* hydrobenzoin. We could thus ascertain that the formation of *erythro* isomer is indeed due to the intramolecular hydride

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(2) Wang, Z.-M.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 8302 and references cited therein.
(3) Singh, V. K. *Synthesis* **1992**, 605.
(4) Maier, G.; Roth, C.; Schmitt, R. K. *Chem. Ber.* **1985**, *118*, 704 and references cited therein.
(5) Surprisingly, aliphatic 1,2-diones yielded *erythro* diols exclusively.
(6) (a) Quallich, G. J.; Woodall, T. M. *Synlett* **1993**, 929. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.

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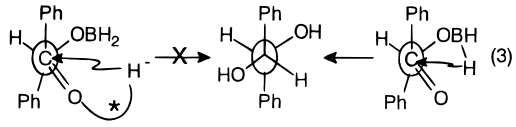
Table 2. Stereoselective Reduction of Diaryl 1,2-Diones

3a - f

Ar	compd	yield[a] (*threo:erythro*)[b]	$[\alpha]_D$[c]	config[d]	% ee[e]
phenyl	**3a**	85 (88:12)	−94.1	*S,S*	>99
4-anisyl	**3b**	80 (89:10)	−118.3	*S,S*	>99
4-tolyl	**3c**	83 (85:15)	−102.5	*S,S*	>99
3-tolyl	**3d**	82 (84:16)	−77.8	*S,S*	>99
2-furyl[f]	**3e**	70 (89:11)	−31.0	*S,S*	>99
2-thienyl[f]	**3f**	80 (92:8)	−49.3	*S,S*	>99

[a] Isolated and purified product. [b] By integration of the benzylic protons in ^{1}H NMR. [c] Of recrystallized product, recorded at 25 °C using $c = 1$ in EtOH. [d] By analogy to the known diol **3a**, ref 9. [e] By ^{1}H NMR (300 MHz) of the diacetate with Eu(hfc)$_3$. [f] Requires 20 mol % of the catalyst **2b** for higher de.

transfer (eq 3). One can thus also rationalize that the faster the rate of the catalyzed reduction the better the diastereoselectivity.



Finally we applied the optimized protocol to the reduction of six representative symmetrical diaryl 1,2-diones, an array of which is easily accessible.[7] As evident from Table 2, very good yields and diastereoselectivity were realized for all the compounds. The diastereomeric purity of the products (except for the diol **3e**) could be easily upgraded by crystallization from MeOH. More gratifying was the fact that the desired stereoisomers (even before crystallization) were of almost 100% ee. Additionally, in all the cases examined, *(S)*-**2b** consistently provided *(S,S)*-(−) enantiomers.

In summary, we have established a convenient catalytic enantioselective route to 1,2-diarylethanediols, many of which are not easily accessible by any known procedure. The utility of this method for the preparation of new chiral ligands useful in asymmetric catalytic reactions can be expected.

Experimental Section

All the reactions were conducted under dry N_2 or Ar atmosphere. THF was freshly distilled over sodium benzophenone. Other anhydrous solvents were obtained following the standard procedure[10] and stored over 4A molecular sieves. The reactions were monitored by TLC using silica gel 60 F_{254} plates, and the products were purified by "flash chromatography" using silica gel 60 (40−63 μM). ^{1}H NMR spectra were recorded at 200 or 300 MHz using TMS as the internal standard in $CDCl_3$. ^{13}C NMR spectra were recorded at 50 MHz with $CDCl_3$ ($\delta = 77$ ppm) as the reference. Neat BMS was purchased from Aldrich, diluted with toluene to 2 M and estimated by gasimmetry. All the starting diones were synthesized following known procedures.[7]

Preparation of Optically Pure (*S,S*)-(−)-1,2-Diaryl-1,2-ethanediols. The following procedure for hydrobenzoin **3a** is representative: To a stirred solution of *(S)*-diphenylprolinol[11] (0.127 g, 0.5 mmol) in anhydrous THF (5 mL) was added BMS (5 mL of 2 M solution in toluene, 10 mmol), and the mixture was stirred while the temperature was maintained at 45 °C for 16 h to obtain a solution of the catalyst **2b**. The resulting mixture was treated dropwise (over a period of 30 min) with a solution of benzil (1.05 g, 5 mmol) dissolved in a minimum volume of anhyd THF (6 mL) at 45 °C. After the addition, the reaction mixture was stirred for 5 min, quenched cautiously with MeOH (1 mL), and stirred for an additional 30 min. Most of the solvent was evaporated and the residue directly chromatographed using EtOAc−hexane (1:9) to obtain chemically pure hydrobenzoin (0.910 g, 85%).

^{1}H NMR analysis of the above product revealed it to be a 88:12 mixture of *threo:erythro* isomers. Furthermore, examination of the corresponding diacetate at 300 MHz using shift reagent Eu(hfc)$_3$ (20 mol %) showed no *(R,R)*-enantiomer within detectable limits. Single crystallization from MeOH provided stereochemically pure *(S,S)*-(−)-hydrobenzoin **(3a)**: mp 148−150 °C (lit.[9] 148−149 °C); $[\alpha]_D$ −94.1 (*c* 1, EtOH) [lit.[9] −94.5 (*c* 0.99, EtOH)]; ^{1}H NMR δ 7.15 (m, 6H), 7.05 (m, 4H), 4.60 (s, 2H), 2.90 (br, 2H).

(S,S)-**3b**: mp 132−134 °C; $[\alpha]_D$ −118.3 (*c* 1, EtOH); ^{1}H NMR δ 7.10 (m, 4H), 6.80 (m, 4H), 4.65 (s, 2H), 3.80 (s, 6H), 2.90 (s, 2H); ^{13}C NMR δ 159.3, 132.4, 128.4, 113.9, 78.9, 55.4; MS *m/z* 274 (M), 137 (base). Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 69.76; H, 6.91.

(S,S)-**3c**: mp 105−107 °C; $[\alpha]_D$ −102.5 (*c* 1, EtOH); ^{1}H NMR δ 7.20−7.10 (m, 8H), 4.70 (s, 2H), 2.95 (br, 2H), 2.35 (s, 6H); ^{13}C NMR δ 137.4, 137.3, 128.8, 127.1, 78.9, 21.3; MS *m/z* 242 (M), 121 (base). Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.30; H, 7.49. Found: C, 79.05; H, 7.59.

(S,S)-**3d**: mp 54−56 °C; $[\alpha]_D$ −77.81 (*c* 1, EtOH); ^{1}H NMR δ 7.40−6.90 (m, 8H), 4.65 (s, 2H), 3.25 (br, 2H), 2.30 (s, 6H); ^{13}C NMR δ 140.3, 137.8, 128.7, 128.1, 127.8, 124.2, 79.0, 21.5; MS *m/z* 242 (M), 122 (base). Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.30; H, 7.49. Found: C, 78.90; H, 7.58.

(S,S)-**3e** (of 78.6% de): viscous liquid; $[\alpha]_D$ −31.0 (*c* 1, EtOH); the compound deteriorates rapidly at ambient temperature. We were therefore unable to crystallize it to upgrade the de or obtain accurate elemental analysis. However, the chemical as well as optical purity was established beyond doubt with the help of LC and spectral data: ^{1}H NMR δ 7.30 (s, 2H), 6.35−6.15 (m, 4H), 4.95 (s, 2H), 4.00 (br, 2H); ^{13}C NMR δ 169.4, 152.9, 142.4, 110.4, 108.0, 69.9; MS *m/z* 176 (M − H_2O), 57 (base).

(S,S)-**3f**: mp 99−100 °C; $[\alpha]_D$ −49.3 (*c* 1, EtOH); ^{1}H NMR δ 7.30 (m, 2H), 6.95 (m, 2H), 6.80 (m, 2H), 5.05 (s, 2H); ^{13}C NMR δ 143.1, 126.8, 125.9, 125.5, 75.0; MS *m/z* 226 (M), 113 (base). Anal. Calcd for $C_{10}H_{10}O_2S_2$: C, 53.07; H, 4.45; S, 28.32. Found: C, 53.23; H, 4.49; S, 27.69.

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(8) While the manuscript for this paper was under preparation, the use of the catalyst **1b** for the reduction of benzil was reported to be 4% de (52:48 for threo:erythro): Quallich, G. J.; Keavey, K. N.; Woodall, T. M. *Tetrahedron Lett.* **1995**, *36*, 4729. This variation of diastereoselectivity can be attributed to the difference in the reaction conditions as compared to those in the present study.

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