Catalytic Enantioselctive Reactions. Part 15.[1] Oxazaborolidine-Catalyzed Asymmetric Reduction of α-Keto Acetals with *N*,*N*-Diethylaniline-Borane (DEANB) Complex

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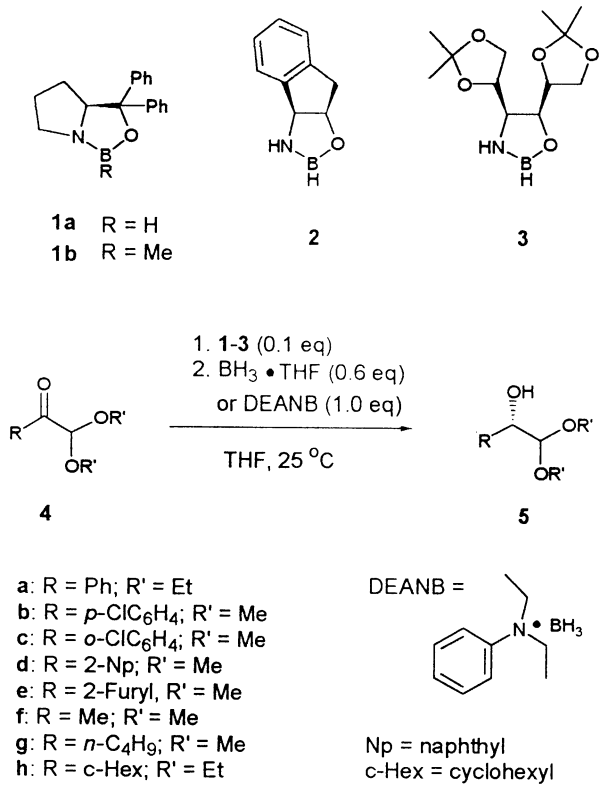
Optically active α-hydroxy aldehydes are not only useful chiral building blocks for synthesis of the natural products, such as rhodianose,[2] rocellaric acid,[3] lipoxine A,[4] *endo*-brevicomine,[5,13b] grayanotoxins[6] and amino sugars[7], but also important substrates for diastereofacial selective reactions of the carbonyl groups, e.g. nucleophilic 1,2-additions or aldol reactions, and cycloadditions.[8] Accordingly, many synthetic methods including transformation of chiral precursors, such as α-hydroxy acids[9] and α-amino acids,[10] biocatalytic reduction[11] or catalytic asymmetric hydrogenation of α-keto (thio)acetals,[12] and asymmetric synthesis from achiral aldehydes[13] have been developed. Recently we reported a stoichiometric asymmetric reduction of α-keto acetals with a chiral borohydride to afford α-hydroxy acetals with high enantioselectivities.[14] Although a number of asymmetric reduction of prochiral ketones catalyzed by oxazaborolidines have been reported,[15] the catalytic asymmetric reduction of α-keto acetals, however, has not been reported to date.[16] Very recently, more practically useful oxazaborolidine-catalyzed asymmetric borane reduction of prochiral ketones using an air-stable borane, *N*,*N*-diethylaniline-borane complex (DEANB) as a reductant has been reported.[17] This prompted us to study the catalytic asymmetric borane reduction of α-keto acetals using this hydride as a borane carrier.

The α-keto acetals used as substrates were prepared from addition of Grignard reagents to dialkoxyacetopiperidides[18] or the reaction of methyl ketones with catalytic amounts of diphenyldiselenide and an excess of ammoniumperoxydisulfate in methanol.[19] Initially, four structurally diverse oxazaborolidines (**1a**[20a], **1b**[20b], **2**[21], and **3**[22]) were selected as representative catalysts for the reduction of 2,2-diethoxy-1-phenylethanone (**4a**). Thus, slow addition of **4a** over 1 h to a solution of 0.6 equiv of borane-THF or 1.0 equiv of DEANB in the presence of 10 mol % of each oxazaborolidine in THF at 25 °C (Scheme 1) afforded 2,2-diethoxy-1-phenylethanol (**5a**) within 10 min in a 97 % yield. The enantiomeric excess of the α-hydroxy acetal **5a** was determined by HPLC analysis using a Chiralcel OD column (eluent: hexane/*i*-PrOH = 40 : 1). Of the oxazaborolidines examined, Corey's CBS reagents (**1**) using DEANB as a borane carrier provided the best enantioselectivity in 96% ee (Table 1, entries 2 and 4). With the same methodology, other aromatic α-keto acetals such as **4b** and **4d** also produced the corresponding α-hydroxy acetals (**5b** and **5d**) with very high optical purities in 99% ee (entries 5 and 7). Interestingly, the reduction of 2,2-dimethoxy-1-(2-chlorophenyl)ethanone (**4c**) provided **5c**



Scheme 1

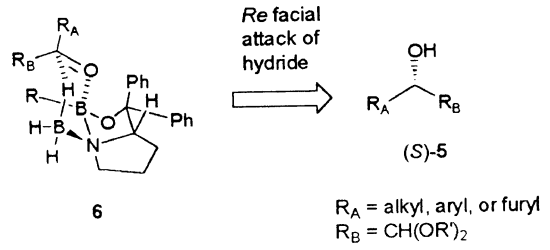
in 30% ee, in contrast to > 99% ee for 2,2-dimethoxy-1-(4-chlorophenyl)ethanone (**4d**) (Table 1, entries 6 and 7). These results indicate the asymmetric induction is sensitive to steric effects of the substituent proximal to the carbonyl group. This is a common phenomenon in oxazaborolidine-catalyzed reduction.[23] A heterocyclic α-keto acetal, 2,2-dimethoxy-1-(2-furyl)ethanone (**4e**), produced the α-hydroxy acetal **5e** with a moderate optical purity (Table 1, entry 8). In the case of aliphatic analogues, the asymmetric reduction afforded somewhat lower enantioselectivities compared with those obtained from aromatic analogues (Table 1, entries 9-13). In all the cases examined, it is noteworthy that the product α-hydroxy acetals (**5**) obtained are consistently enriched in the *S*-enantiomers. The stereochemical course of the asymmetric reduction can be explained by the proposed mechanism involving a transition state **6**, where the α-keto acetals are attacked by hydride on their *Re* faces to provide (*S*)-α-hydroxy acetals (Scheme 2).[20,24]

In summary, we have developed a practically useful synthetic method for chiral α-hydroxy acetals by oxazaboroloi-

Table 1. Oxazaborolidine-Catalyzed Borane Reduction of α-Keto Acetals in THF at 25 °C[a]

entry	compd	cat (0.1 eq)	borane	5			
				yield (%)[c]	$[\alpha]^{23}_D$	% ee	config
1	**4a**	**1a**	BH_3-THF (0.6 eq)	97	+18.40 (*c* 5.02, $CHCl_3$)	92[d]	*S*[k]
2	**4a**	**1a**	DEANB[b] (1.0 eq)	99	+19.22 (*c* 5.11, $CHCl_3$)	96[d]	*S*[k]
3	**4a**	**1b**	BH_3-THF (0.6 eq)	96	e	91[d]	*S*[k]
4	**4a**	**1b**	DEANB (1.0 eq)	98	+19.21 (*c* 5.01, $CHCl_3$)	96[d]	*S*[k]
5	**4b**	**1b**	DEANB (1.0 eq)	91	+11.14 (*c* 5.41, $CHCl_3$)	>99[f]	*S*[l]
6	**4c**	**1b**	DEANB (1.0 eq)	99	+7.11 (*c* 5.41, $CHCl_3$)	30[f]	*S*[l]
7	**4d**	**1b**	DEANB (1.0 eq)	97	+2.64 (*c* 5.11, $CHCl_3$)	99[g]	*S*[l]
8	**4e**	**1b**	DEANB (1.0 eq)	85	+3.68 (*c* 4.80, $CHCl_3$)	71[h]	m
9	**4f**	**1a**	BH_3-THF (0.6 eq)	63	e	58[i]	*S*[n]
10	**4f**	**1a**	DEANB (1.0 eq)	65	-8.38 (*c* 3.11, MeOH)	60[i]	*S*[n]
11	**4f**	**1b**	DEANB (1.0 eq)	63	e	60[i]	*S*[n]
12	**4g**	**1b**	DEANB (1.0 eq)	73	-20.51 (*c* 1.15, CH_2Cl_2)	42[h]	*S*[o]
13	**4h**	**1b**	DEANB (1.0 eq)	93	-10.98 (*c* 4.11, CH_2Cl_2)	66[j]	*S*[p]

[a] [compd] = 0.3 M in the case using BH_3-THF (0.6 eq); [compd] = 0.6 M in the case using DEANB. [b] DEANB = *N*,*N*-Diethyaniline-borane complex. [c] Isolated yield. [d] By HPLC analysis with a Chiralcel OD using hexane/2-propanol (40 : 1) as eluent. [e] Not measured. [f] By HPLC analysis with a Chiralcel OD using hexane/2-propanol (9 : 1) as eluent. [g] By HPLC analysis with a Chiralcel OT using hexane/2-propanol (9 : 1) as eluent. [h] By GC analysis using a 20 m Chiraldex GTA column. [i] By GC analysis of its (-)-menthyl carbonate using a 25 m Supelcowax™ 10 capillary column. [j] By GC analysis of its (*R*)-MTPA ester using a 25 m Supelcowax™ 10 capillary column. [k] Based on (*S*)-(+)-1-phenyl-2,2-dimethoxyethanol: ref. 11a and 14. [l] Absolute configuration is unknown, but probably *S*, based on comparison of the order of elution of HPLC and/or the sign of optical rotation with those of aromatic analogues: ref. 14. [m] Unknown. [n] Based on (*R*)-(+)-1,1-dimthoxy-2-propanol: ref. 12. [o] Based on (*S*)-(-)-1,1-dimethoxy-2-hexanol: ref. 11a. [p] Absolute configuration is unknown, but probably *S*, based on comparison of the order of elution of GC analysis and/or the sign of optical rotation with those of aliphatic analogues: ref. 14.



Scheme 2

dine-catalyzed asymmetric reduction of α-keto acetals using an air stable *N*,*N*-diethylaniline-borane complex (DEANB) as a borane source. This is the first example to obtain aromatic α-hydroxy acetals with high enantioselectivity approaching 100% ee. Further applications using this methodology are now under investigation. In a typical procedure, the asymmetric reduction of **4b** is representative. To a solution of **1b** (0.1 mmol; 0.2 M, 0.5 mL) in dry THF was added DEANB (1 mmol, 163 mg, neat 0.18 mL) at 25 °C. To this was added slowly 1.1 mL of THF solution of **4b** (1 mmol; 215 mg) over a period of 1 h using a syringe pump at 25 °C. The reaction mixture was stirred for 10 min at the same temperature and then quenched cautiously with methanol (0.5 mL). Solvent was evaporated under reduced pressure and the product was further purified by a flash column chromatography on silica gel (230-400 mesh) using ethyl acetate/hexane (1 : 2) as eluent to give **5b** (197 mg, 91%); R_f 0.43; syrup (Found: C, 55.41; H, 6.10; Cl, 16.37. $C_{10}H_{13}ClO_3$ requires C, 55.44; H, 6.05; Cl, 16.36); $[\alpha]^{23}_D$ +11.14 (*c* 5.41 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3436, 2930, 1597, 1490, 1187, 1120, 1076, 1012, 972, 823. ^{1}H NMR (400 MHz; $CDCl_3$; Me_4Si) δ 2.72, (1H, br s, O*H*), 3.29 (3H, s, OC*H*$_3$), 3.42 (3H, s, OC*H*$_3$), 4.23 (1H, d, *J* = 6.5, C*H*OH), 4.59 (1H, d, *J* = 6.4, C*H*(OMe)$_2$), 7.31-7.37 (4H, m, Ar*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ 137.87 (Ar *C*), 133.63 (Ar *C*), 128.47 (Ar *C*), 128.37 (Ar *C*), 107.54 (MeO*C*HOMe), 73.32 (*C*HOH), 56.23 (*C*H$_3$O), 55.00 (*C*H$_3$O). HPLC analysis of the product **5b** with a Chiralcel OD column using hexane/2-propanol (9 : 1) as eluent showed a composition 99.9% of *S*-isomer and 0.1% of *R*-isomer (*i.e*., 99.8% ee).

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