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A convenient method for the preparation of oxazaborolidine catalyst in situ using (*S*)-α,α-diphenylpyrrolidinemethanol, tetrabutylammonium borohydride, and methyl iodide for the asymmetric reduction of prochiral ketones

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Abstract—An oxazaborolidine catalyst is readily prepared in situ at 25 °C in THF using (*S*)-α,α-diphenylpyrrolidinemethanol and borane generated from tetrabutylammonium borohydride/CH_3I reagent system. The oxazaborolidine/BH_3 reagent system prepared in this way is useful for the reduction of prochiral ketones to the corresponding alcohols with up to 99% ee.

1. Introduction

The synthesis of enantiomerically pure compounds has become an important area of research for pharmaceutical industries, as often two enantiomers of a chiral drug molecule display different biological activities.[1] Asymmetric reduction of prochiral ketones is an extremely important methodology for the synthesis of chiral secondary alcohols. The oxazaborolidine (CBS reagent)-catalyzed asymmetric reduction methodology has been extensively used for this purpose.[2–4] Even though the parent catalyst H-CBS **4**, prepared in situ using α,α-diphenylpyrrolidinemethanol and BH_3–THF, has been found to give good results in asymmetric reductions, the corresponding B-methyl derivative is preferred. However, this reduction method is not entirely satisfactory, particularly for large-scale productions, owing to the requirement for trimethyl boroxine[5a] or methyl boronic acid[5b] and the requirement of complete removal of water from such condensations to avoid undesired effects.[6] The other difficulty is the requirement of the highly reactive reagents, such as borane–THF,[7] borane–SMe_2,[8] borane–1,4-thioxane,[9] catecholborane,[10] and *N*,*N*-diethylaniline–borane[11] (DEANB) complexes for the oxazaborolidine catalyzed asymmetric reduction of ketones. Although several of these borane complexes are commercially available, these borane carriers suffer from drawbacks with regards to their commercial application because of difficulties in handling and transporting these reagents, especially for large scale applications. We have reported from this laboratory that borane–THF prepared in situ using $NaBH_4$ and I_2 in THF is useful for several synthetic applications that require borane–THF. Unfortunately, the α,α-diphenylpyrrolidinemethanol and $NaBH_4$/I_2 combination gave poor results in the asymmetric reduction of acetophenone.[12] It was thought that a major problem in using $NaBH_4$ is that it is only sparingly soluble in THF. Accordingly, we have undertaken an investigation to employ the readily accessible $R_4N^+BH_4^-$ for this purpose. Herein we report that the $R_4N^+BH_4^-$, CH_3I and (*S*)-α,α-diphenylpyrrolidinemethanol combination is useful for the asymmetric reduction of aryl alkyl ketones to obtain the corresponding alcohols in up to 99% ee (Fig. 1).

2. Results and discussion

The $R_4N^+BH_4^-$ species has been reported to have low reactivity as a reducing agent.[13] This is easily realized by the fact that it can be recrystallized from either ethyl acetate or even acetone if the operation is carried out rapidly. This reagent had been known for some time and it has been used for the reduction of a number of representative carbonyl functionalities. However, it has not been employed

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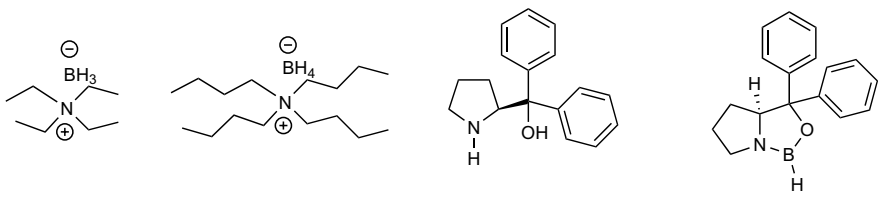
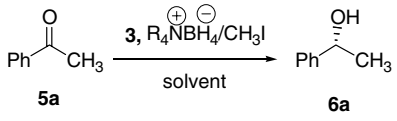


Figure 1.

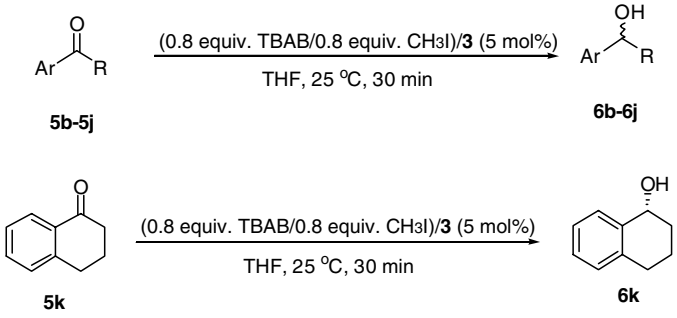
in an asymmetric reduction in combination with chiral α,α-diphenylpyrrolidinemethanol. We have observed that the tetrabutylammonium borohydride (TBAB **2**)/CH_3I reagent system in the presence of (*S*)-α,α-diphenylpyrrolidinemethanol (5 mol %) affords a very easy and simple preparation of the oxazaborolidine catalyst **4**, as well as the BH_3 species, which effectively reduces acetophenone within about 30 min at 25 °C (Scheme 1, Table 1).



Scheme 1.

Initially, we examined the reduction of acetophenone using the tetraethylammonium borohydride (TEAB **1**)/CH_3I combination under the influence of (*S*)-α,α-diphenylpyrrolidinemethanol **3** (20 mol %) in DCM at 0 °C. In this case, the desired alcohol was obtained in quantitative yields with 63% ee (Table 1, entry 1). Surprisingly, at 25 °C, the ketone remained unreacted. The same result was observed when THF was used as a solvent, as the TEAB **1** is insoluble in THF at room temperature. Fortunately, the more soluble TBAB **2** gave better results. We observed that the TBAB **2**/CH_3I reagent system in the presence of catalyst **3** (20 mol %) yielded the desired alcohol in 97% ee (Table 1, entry 2). The use of I_2 in place of CH_3I, or a change of solvent led to a decreased ee (Table 1, entries 3 and 4). In the absence of additives (CH_3I and I_2), the acetophenone remained unaffected. Upon the addition of CH_3I, evolution of CH_4 was noticed, indicating that the formation of BH_3·THF in situ from tetraalkylammonium borohydride is essential for the reduction. Chiral aminoalcohol **3** can be used in 5 mol % in THF to give maximum selectivity (Table 1, entries 5–9).

With a view to extend the scope and to understand the applicability of this reagent system, we examined the reduction of representative class of aryl alkyl ketones using 5 mol % catalyst **3** and obtained the secondary alcohols **6b–k** in 41–96% ee (Scheme 2, Table 2).



Scheme 2.

The *para*-substituted acetophenones are reduced to give 93–96% ee as observed in the reductions using the B-methyl CBS catalyst system.[6] The ee's are not affected significantly by alkyl groups of the acetophenone and electron donating

Table 1. Enantioselective reduction of acetophenone **5a** at various conditions[a]

Entry	Reagent (equiv)	Additive (equiv)	Catalyst **3** (mol %)	Solvent	Temperature (°C)	Yield[b] (%)	Conf.[c]	ee[d] (%)
1	TEAB **1** (1)	CH_3I (1)	20	CH_2Cl_2	0	76	(*R*)	63
2	TBAB **2** (1)	CH_3I (1)	20	THF	25	86	(*R*)	97
3	TBAB **2** (1)	I_2 (0.5)	20	THF	25	78	(*R*)	89
4	TBAB **2** (1)	CH_3I (1)	20	Toluene	25	68	(*R*)	47
5	TBAB **2** (1)	CH_3I (1)	5	THF	25	87	(*R*)	96
6	TBAB **2** (1)	CH_3I (1)	5	THF	25	85	(*R*)	84
7	TBAB **2** (0.8)	CH_3I (0.8)	2	THF	25	88	(*R*)	97
8	TBAB **2** (0.8)	CH_3I (0.8)	1	THF	25	86	(*R*)	87
9	TBAB **2** (0.8)	CH_3I (0.8)	5	THF	25	89	(*R*)	>99

[a] All reactions were carried out using 5 mmol of (TEAB **1** or TBAB **2**), 5 mmol of CH_3I, 5 mmol of ketone in 25 mL of solvent except for entries 7–9 where 4 mmol of TBAB **2**, 4 mmol of CH_3I, and 5 mmol of ketone were used.

[b] The yields are of the isolated products after purification by column chromatography. The products were identified by spectral data (IR, ^1H NMR and ^{13}C NMR) and physical constant data.

[c] Absolute configuration was assigned by the comparison of the sign of the specific rotation with that of a literature value.

[d] Determined by HPLC analysis using the chiral column, Chiralcel-OD-H.

Table 2. Asymmetric reduction of representative ketones[a]

Substrate	Ar	R	Product	Yield[b] (%)	Conf.[c]	ee (%)
5b	4-Methylphenyl	CH_3	**6b**	88	(R)	96[d]
5c	4-Nitrophenyl	CH_3	**6c**	82	(*R*)	93[e]
5d	4-Bromophenyl	CH_3	**6d**	89	(*R*)	95[d]
5e	4-Chlorophenyl	CH_3	**6e**	89	(*R*)	96[d]
5f	Phenyl	C_2H_5	**6f**	87	(*R*)	91[f]
5g	Phenyl	C_3H_7	**6g**	89	(*R*)	94[g]
5h	Phenyl	CH_2Cl	**6h**	79	(*S*)	82[f]
5i	Phenyl	CH_2Br	**6i**	76	(*S*)	76[f]
5j	Phenyl	$C(Ph)_2OH$	**6j**	78	(*R*)	41[h]
5k	α-Tetralone		**6k**	76	(*R*)	67[f]

[a] All reactions were carried out using 4 mmol of TBAB **2**, 4 mmol of CH_3I, and 5 mmol of ketone in the presence of **3** (5 mol %) in THF (25 mL) for 30 min and stirred at 25 °C.

[b] The yields are of the isolated products after purification by column chromatography. The products were identified by spectral data (IR, ^1H NMR, and ^{13}C NMR) and physical constant data.

[c] Absolute configuration was assigned by comparison of the sign of the specific rotation with that of a literature value.

[d] Determined by HPLC analysis using the chiral column, Chiralcel-OJ-H.

[e] Based on reported maximum[14] $[\alpha]_D^{25} = +31.0$ (*c* 1.22, MeOH) for (*R*)-isomer.

[f] Determined by HPLC analysis using the chiral column, Chiralcel-OD-H.

[g] Based on reported maximum[15] $[\alpha]_D^{25} = +45.2$ (*c* 3.0, benzene) for (*R*)-isomer.

[h] Based on reported maximum[16] $[\alpha]_D^{25} = +223.6$ (*c* 1.32, $CHCl_3$) for (*R*)-isomer.

or withdrawing nature of the aromatic substituent (Table 2, ketones **5b**–**g**). α-Haloketones were reduced with moderate to good enantioselectivities (Table 2, ketones **5h** and **5i**). However, asymmetric induction was low for the reduction of the cyclic ketone **5k**. This was presumably due to competing uncatalyzed reduction. This was similar to ketone **5j** possessing steric bulk around the prochiral carbonyl group, which therefore may find it difficult to anchor onto the oxazaborolidine catalyst.[3]

3. Conclusion

In conclusion, the asymmetric reduction of prochiral ketones using TBAB **2**/CH_3I reagent system gave the corresponding chiral secondary alcohol in good selectivity. This method offers a relatively simple and inexpensive approach to this widely used transformation in syntheses.

4. Experimental

4.1. General procedure for the asymmetric reduction of acetophenone utilizing the TBAB 2/CH_3I reagent system

Tetrabutylammonium borohydride **2** (1.02 g, 4 mmol) and (*S*)-α,α-diphenylpyrrolidinemethanol (0.06 g, 0.25 mmol) in THF (12 mL) were taken in a two neck RB flask. The contents were stirred at 25 °C for 15 min under an N_2 atmosphere. Methyl iodide (0.56 g, 0.25 mL, 4 mmol) was added using a syringe and the reaction mixture was stirred for about 30 min. Acetophenone (0.60 g, 0.58 mL, 5 mmol) in THF (12 mL) was added dropwise through a pressure equalizer for about 30 min under an N_2 atmosphere. The reaction mixture was stirred until the ketone had disappeared. The mixture was carefully quenched with 3 M HCl (10 mL). The organic layer was extracted with ether (3×30 mL). The combined organic extract was washed with brine (30 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated to give a yellow residue. The residue was purified on a silica gel column to obtain the (*R*)-1-phenylethanol using hexane/ethyl acetate (97:3) as eluent.

4.2. Procedure utilizing TBAB 2/I_2 reagent system

Tetrabutylammonium borohydride **2** (1.02 g, 4 mmol) and (*S*)-α,α-diphenylpyrrolidinemethanol (0.06 g, 0.25 mmol) in THF (12 mL) were taken in a two neck RB flask. The contents were stirred at 25 °C for 5 min under an N_2 atmosphere. I_2 (0.50 g, 2 mmol) dissolved in THF (12 mL) was added slowly for about 15–20 min through a pressure equalizer at 0 °C under an N_2 atmosphere and the reaction mixture was allowed to stir at 0 °C for about 30 min. The reaction mixture was then slowly brought to 25 °C and was stirred for about 10 min under an N_2 atmosphere. Acetophenone (0.60 g, 0.58 mL, 5 mmol) in THF (15 mL) was added dropwise through a pressure equalizer for about 30 min. The reaction mixture was stirred until the ketone had disappeared. The mixture was carefully quenched with 3 M HCl (10 mL). The organic layer was extracted with ether (3×30 mL). The combined organic extract was washed with brine (30 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated to give a yellow residue. The residue was purified on a silica gel column chromatography to obtain the (*R*)-1-phenylethanol using hexane/ethyl acetate (97:3) as eluent.

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