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Enantioselective reduction of trifluoromethyl ketones using an oxazaborolidine catalyst generated in situ from a chiral lactam alcohol

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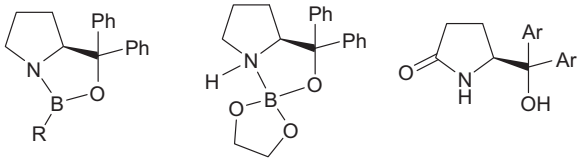
ABSTRACT

The oxazaborolidine catalyst prepared in situ from the chiral lactam alcohol **2** and borane was found to catalyze the enantioselective reduction of highly reactive trifluoromethyl ketones at room temperature with high enantioselectivities of up to 86% ee.

1. Introduction

The oxazaborolidine-catalyzed asymmetric borane reduction of prochiral ketones (CBS reduction) has become important in modern synthetic chemistry since the reports of Itsuno et al.[1] and Corey et al.[2] The CBS reduction provides a predictable absolute stereochemistry and high enantiomeric excess (ee) of chiral secondary alcohols, which are valuable chiral building blocks for the synthesis of natural products.

As an alternative method, we have previously reported that the oxazaborolidine catalyst can be generated in situ from the chiral lactam alcohol **2**, (*S*)-5-(diphenylhydroxymethyl)pyrrolidin-2-one (Fig. 1), and borane–tetrahydrofuran (BH_3–THF) at room temperature; the resulting oxazaborolidine was found to catalyze the borane reduction of aromatic ketones with high enantioselectivities of up to 98% ee.[3] Moreover, we developed the enantioselective reduction of aliphatic ketones, which was carried out using the oxazaborolidine **1e** generated in situ from the chiral lactam alcohol **3** and 4-iodophenoxyborane (4-I-$PhOBH_2$).[4] Fluorine-containing optically active alcohols have recently been studied for preparing ferroelectric liquid crystals, but the trifluoromethyl ketones are so reactive that reduction using the CBS catalyst generally affords the corresponding alcohols with poor enantioselectivity.[5] However, Corey et al.[6] reported that the reduction of trifluoroacetophenone with Bu–CBS **1c** and 2 equiv of catecholborane at −78 °C proceeded with a 90% ee (*R*). On the other hand, Stepanenko et al.[7] described that the reduction of trifluoroacetophenone using spiroborate esters **1g** and BH_3–Me_2S at room temperature provided a slightly lower enantioselectivity (82% ee) and the opposite enantioselection (*S*). Recently, Korenaga et al.[8] also reported that the electronic tuning of the CBS catalyst **1f** could enhance the enantioselectivity up to 90% ee (*S*). Herein, we report the practical enantioselective reduction of trifluoromethyl ketones using the simple oxazaborolidine **1a**, without steric and electronic factors, generated in situ from the chiral lactam alcohol **2** and borane (Scheme 1).



1a R = H
1b R = Me
1c R = *n*-Bu
1d R = OMe
1e R = O-4-I-C_6H_4
1f R = 2,4,6-$F_3C_6H_2$

1g

2 Ar = Ph
3 Ar = 3,5-Me_2Ph

Figure 1.

2. Results and discussion

We first examined the effect of borane reagents on the enantioselectivity of the reduction of trifluoroacetophenone. Chiral lactam alcohol **2**[3] or **3**[4] (10 mol %) was added to various borane reagents, such as BH_3–THF, borane–dimethylsulfide (BH_3–Me_2S), catecholborane, and 4-I-$PhOBH_2$, at room temperature and stirred for 10 min, except for 4-I-$PhOBH_2$, which was stirred for 1 h. To the resulting oxazaborolidine catalyst, a solution of trifluoroacetophenone was added slowly over 1 h using a syringe pump, providing chiral secondary alcohols in good yields. The results are summarized in Table 1. The reduction using **2** and BH_3–THF afforded the (*S*)-alcohol with a moderate enantioselectivity (52% ee, entry 1), although the reduction with BH_3–Me_2S and catecholborane provided no enantioselectivity (entries 2 and 3).

Using the more bulky chiral lactam alcohol **3** or 4-I-$PhOBH_2$ did not increase the enantioselectivity (entries 4 and 5), which is effec-

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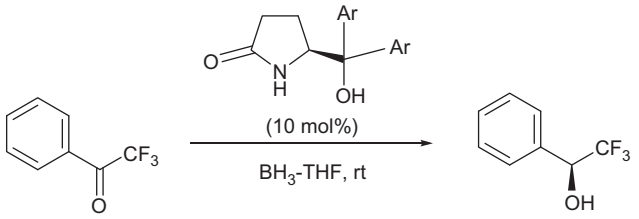


Scheme 1.

Table 1
Asymmetric reduction of trifluoroacetophenone using chiral lactam alcohol 2 or 3[a]

Entry	Ligand	Borane	Solvent	Yield[b] (%)	% ee[c]	Config.[d]
1	**2**	BH_3–THF	THF	89	52	(*S*)
2	**2**	BH_3–Me_2S	THF	77	3	(*R*)
3	**2**	Catecholborane	THF	36	2	(*S*)
4	**3**	BH_3–THF	THF	90	46	(*S*)
5	**3**	4-I-PhOBH_2	THF	67	42	(*S*)
6	**2**	BH_3–THF	Toluene	82	56	(*S*)
7	**2**	BH_3–THF	CH_2Cl_2	97	78	(*S*)
8	**2**	BH_3–THF	$CHCl_3$	90	80	(*S*)
9	**2**	BH_3–THF	CCl_4	56	8	(*S*)

[a] All reactions were carried out with 10 mol % of **2** or **3** and 1.0 equiv of BH_3–THF at rt for 1 h.
[b] Isolated yield.
[c] Determined by HPLC analysis using a Chiralcel OD column.
[d] Determined by comparison of the retention time of commercial (*S*)-2,2,2-trifluoro-1-phenylethanol.

tive for the reduction of aliphatic ketones.[4] It should be noted that a solvent effect was observed during the reduction with **2** and BH_3–THF in various solvents (entries 6–9). Toluene showed a slight increase in the ee (entry 6), while the polar solvents dichloromethane (CH_2Cl_2) and chloroform ($CHCl_3$) afforded higher enantioselectivities (78%, 80% ee, entries 7 and 8, respectively).[9] When the less polar carbon tetrachloride was used as the solvent, the enantioselectivity decreased significantly (entry 9). The stereochemistry of the resulting secondary alcohol was (*S*) except in the case of entry 2, which was in agreement with that of the reduction catalyzed by **1f**[8] and **1g**.[7] These results suggest that a polar reaction solvent is crucial to reduce trifluoroacetophenone using **1a** with a high enantioselectivity, probably due to its stabilization of the preferred transition state **A**, which is the same for acetophenone (Fig. 2).

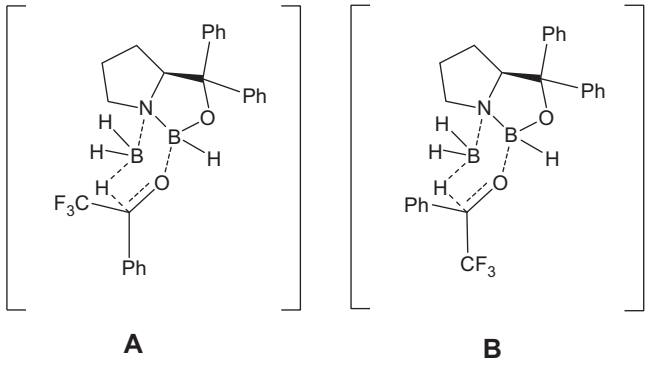


Figure 2. Proposed transition state models.

To further improve the enantioselectivity of trifluoroacetophenone reduction, we investigated the temperature effect, the effect of borane equivalents and catalyst loading on the enantioselectivity. The reduction was carried out with BH_3–THF in $CHCl_3$. The results are summarized in Table 2. When the reaction temperature was decreased from 25 to 0 °C and −40 °C, the ee of the resulting secondary alcohol greatly decreased to 8% ee and 18% ee, respectively, with the opposite enantioselection (entries 1–3). At −78 °C, the reaction did not take place. On the other hand, the same enantioselectivity was obtained when the reaction was carried out at 40 °C (entry 4). This temperature effect is in accordance with the reported one[8] for the reduction of trifluoroacetophenone but is quite different from the reduction of acetophenone (97% ee at −10 °C).[3] At low temperature, the transition state **B** might be increased due to electronic repulsion between the trifluoromethyl group and lone pair of the carbonyl group as proposed by Corey et al.[6] and, therefore, the reverse of the sense of enantioselectivity might be observed. It should be noted that we observed that the enantioselectivity was susceptible to the balance between the borane equivalents and catalyst loading. When 1.2 equiv of BH_3–THF was used, the ee was significantly decreased (entry 5). On the other hand, using 0.8 equiv of BH_3–THF increased the enantioselectivity up to 83% ee (entry 6). In addition, catalyst **1a** showed the same enantioselectivity even with an 8 mol % ligand loading when 0.64 equiv of BH_3–THF was used (entry 9).

Table 2
The temperature effect and effect of borane equivalents on the enantioselectivity for reduction of trifluoroacetophenone using **2**[a]

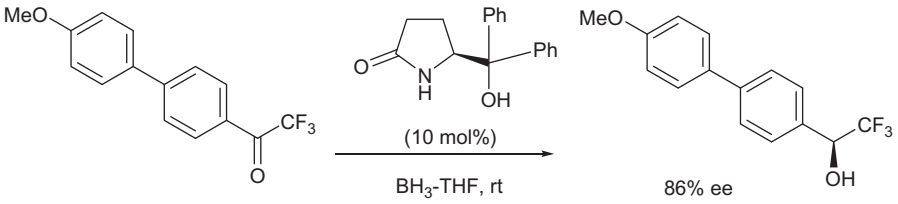
Entry	Ligand (mol %)	BH_3 (equiv)	Temp (°C)	Yield[b] (%)	%ee[c]	Config.[d]
1	10	1.0	−40	56	18	(*R*)
2	10	1.0	0	87	8	(*R*)
3	10	1.0	25	90	80	(*S*)
4	10	1.0	40	97	80	(*S*)
5	10	1.2	25	98	74	(*S*)
6	10	0.8	25	96	83	(*S*)
7	10	0.6	25	93	81	(*S*)
8	8	0.8	25	93	82	(*S*)
9	8	0.64	25	90	83	(*S*)

[a] All reactions were carried out with 10 mol % of **2** and BH_3–THF in $CHCl_3$ for 1 h except for entry 1, in which the reaction was carried out for 4 h.
[b] Isolated yield.
[c] Determined by HPLC analysis using a Chiralcel OD column.
[d] Determined by comparison of the retention time with commercial (*S*)-2,2,2-trifluoro-1-phenylethanol.

Finally, we carried out the catalytic reduction of 4-methoxy-4′-(trifluoroacetyl)biphenyl, which is a potentially interesting precursor for the preparation of ferroelectronic liquid crystals.[10] As shown in Scheme 2, the more sterically hindered biphenyl trifluoromethyl ketones were reduced under the optimized reaction conditions (BH_3–THF, $CHCl_3$, 25 °C) with a higher enantioselectivity (86% ee) than trifluoroacetophenone in 87% yield, which is the same enantioselectivity as the reduction with Bu–CBS **1c** or the oxazaborolidine derived from L-threonine and catecholborane in CH_2Cl_2–toluene at −90 °C, but with an opposite (*S*)-configuration.[10]

3. Conclusion

In conclusion, we have demonstrated that a simple oxazaborolidine catalyst[11] generated in situ from the chiral lactam alcohol **2** and BH_3–THF catalyzed the enantioselective reduction of trifluoromethyl ketones in $CHCl_3$ at room temperature with high enantioselectivity. It is interesting to note that the polar halogenated organic solvent, $CHCl_3$, is the optimal solvent for achieving high enantioselectivities of the reactive trifluoromethyl ketones, because CH_2Cl_2 has generally been reported to afford a somewhat lower ee than THF and toluene for the asymmetric reduction of typical ketones. Thus, this method offers an excellent alternative for the asymmetric reduction of trifluoromethyl ketones. Moreover, this practical methodology has many advantages that include stability toward air and



Scheme 2. Enantioselective reduction of 4-methoxy-4′-(trifluoroacetyl)biphenyl using **2**.

moisture and the requirement of mild reaction conditions compared to the reported methods for trifluoromethyl ketones.[6–8] Further applications of this asymmetric catalytic reduction of *para*-substituted biphenyl trifluoromethyl ketones are currently in progress.

4. Experimental

4.1. General

The ^{1}H NMR and ^{13}C NMR spectra were recorded at 600 and 150 MHz using a JNM-ECA600 spectrometer, respectively. The mass spectra were recorded by a JEOL JMS-SX102A mass spectrometer. Optical rotations were taken with a JASCO P-1010 polarimeter. HPLC analysis was carried out using a DAICEL Chiralcel OD column (0.46 × 25 cm) with a Shimadzu LC6A. THF and toluene were dried over benzophenone ketyl before use. CH_2Cl_2 and $CHCl_3$ were dried over P_2O_5 before use. TLC was carried out on Merck glass plates precoated with Silica Gel 60F-254 (0.25 mm), and column chromatography was performed using Merck 23–400 mesh silica gel. BH_3–THF was purchased from Toyo Kasei Kogyo Co. and BH_3–Me_2S and catecholborane were purchased from Aldrich Chemical. All other reagents were purchased from the Wako Chemical Co.

4.2. Typical procedure for the reduction of a trifluoromethyl ketone

To a solution of chiral lactam alcohol **2** (10.7 mg, 0.04 mmol, 10 mol %) in $CHCl_3$ (0.8 ml) was added a 1 M BH_3–THF solution (0.48 ml, 0.48 mmol). The mixture was stirred under Ar at room temperature for 10 min. A solution of trifluoroacetophenone (56 μl, 0.4 mmol) in $CHCl_3$ (0.6 ml) was added dropwise over 1 h using a syringe pump. The reaction mixture was stirred until the ketone disappeared based on TLC (1 h). The reaction was quenched with MeOH (200 μl), extracted with ether and dried over $MgSO_4$. Flash-chromatography of the crude mixture (hexane/AcOEt, 5:1) gave (*S*)-2,2,2-trifluoro-1-phenylethanol (63.4 mg, 90%). The ee was determined to be 83% by HPLC analysis using a Chiralcel OD column, hexane/*i*-PrOH = 97:3, 1.0 ml/min, and the absolute configuration was established by comparing the retention time of the commercially available (*S*)-2,2,2-trifluoro-1-phenylethanol [retention times = 22 and 27 min for (*S*) and (*R*), respectively].

4.3. (*S*)-2,2,2-Trifluoro-1-(4-methoxy-4′-biphenyl)ethanol

Yield 87%, $[\alpha]_D^{25} = +22.7$ (*c* 0.08, $CHCl_3$) {lit.[12] $[\alpha]_D^{23} = +26.0$ (*c* 0.19, $CHCl_3$), 98% ee for the (*S*)-form}. The ee was determined to be 86% by HPLC analysis using a Chiralcel OD column, hexane/*i*-PrOH = 90:10, 1.0 ml/min [retention times = 12 and 20 min for (*S*) and (*R*), respectively].[10] Mp 130–132 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.69 (br s, 1H), 3.86 (s, 3H), 5.07 (q, *J* = 6.90 Hz, 1H), 6.99 (d, *J* = 8.28 Hz, 2H), 7.49–7.55 (m, 4H), 7.60 (d, *J* = 8.28 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 55.4, 72.5 (q, *J* = 50.3 Hz), 114.3, 124.3 (q, *J* = 281.5 Hz), 126.9, 127.8, 128.2, 132.1, 132.8, 141.2, 159.5.

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