Rational electronic tuning of CBS catalyst for highly enantioselective borane reduction of trifluoroacetophenone†

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α,α,α-Trifluoroacetophenone (2), which is susceptible to non-catalytic reduction by BH_3, could be reduced to chiral alcohol up to 90% ee by using electronically tuned-CBS catalyst (1) with BH_3. The enantioselectivities highly correlated with the differential orbital energies between 1–BH_3 adduct and 2, which were calculated by DFT method.

In asymmetric catalysis, the enantioselectivity of the reaction product is generally controlled by steric repulsion between asymmetric catalyst and substrate. The electronic effect of a ligand substituent in the catalyst[1] or substrate[2] can play an important role in this phenomenon. Among asymmetric catalysts, the Corey–Bakshi–Shibata (CBS) catalyst (**1**) and other oxazaborolidine (OAB) catalysts are useful for achieving the asymmetric reduction of ketones.[3] In asymmetric BH_3 reductions using these catalysts, the enantioselectivity of the product can be affected by introducing electron-donating or -withdrawing substituents into the catalyst or substrate.[4] Reduction of ketonic substrates bearing electron-withdrawing groups (EWGs) tends to afford products with relatively low enantioselectivity.[5] In particular, OAB-catalyzed asymmetric BH_3 reduction of α,α,α-trifluoroacetophenone (**2**) gives α-(trifluoromethyl)benzyl alcohol (**3**) with poor enantio-selectivity;[6,7] when the OAB catalyst is the popular CBS catalyst *B*-Me–(*S*)-CBS (**1a**), our preliminary study shows that reaction gives **3** with only 2% ee. This low value is attributed to the anomalous electronic nature of **2**[8] rather than to its undiscriminating nature in the transition state. The $\pi^{*C=O}$ orbital energy of **2** (LUMO = −2.46 eV) is much lower than that of acetophenone (LUMO = −1.69 eV) and similar to that of activated acetophenone formed by catalysis with CBS (LUMO = −2.52 eV) (Fig. 1).[9] These results indicate that **2** is a highly reactive substrate for BH_3 reduction without catalyst. Furthermore, the n^O orbital energy of **2** (HOMO − 2 = −7.85 eV) is much lower than that of acetophenone (HOMO = −6.94 eV) (Fig. 1),[9] indicating the difficulty of coordinating **2** to the CBS catalyst. As a result, noncatalytic reduction of **2** with BH_3 occurs before coordination to the catalyst, giving racemic **3**. Therefore, we speculated that highly enantioselective BH_3 reduction of **2** requires a CBS catalyst with high Lewis acidity to form a catalyst–**2** adduct. In this communication, we attained the asymmetric BH_3 reduction of **2** with high enantioselectivity by means of an electron-tuned CBS catalyst. The electronic effect was investigated by Density Functional Theory (DFT) calculations.

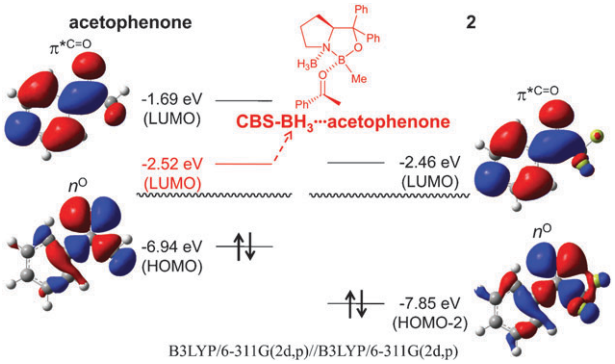

Fig. 1 Comparison of HOMO and LUMO between **2** and acetophenone.

To control the Lewis acidity of the CBS catalyst, we modified its *B*-aryl group by introducing EWGs (Fig. 2). The steric effect of functional groups on *B*-aryl seems to not greatly influence the transition state of the asymmetric reduction.[10] Therefore, introducing varying numbers of fluoro-functional groups into *B*-aryl allows fine electronic tuning of the catalyst without significantly affecting the transition state. We easily prepared CBS catalysts **1b–1h** from (*S*)-α,α-diphenyl-2-pyrrolidinemethanol and the corresponding arylboronic acid by the conventional method, and prepared **1i** by an alternative method.[11] Asymmetric BH_3 reduction of **2** was performed by catalysis with 10% *B*-R–(*S*)-CBS (**1**) at 30 °C for 1 h (Table 1). In all cases, the product (*S*)-**3** was obtained quantitatively. The enantioselectivity of **3** was greatly improved by changing the substituent on the boron atom of **1** from Me to Ar (entry 1 *vs.* 2–9). The highest enantioselectivity was obtained with **1h** (entry 8). Interestingly, the enantio-sense of **3** was opposite to that of the product of the same reaction catalyzed by *B*-^{n}Bu–(*S*)-CBS with catecholborane as the reducing agent.[7] In our catalytic system, asymmetric introduction to ketone **2** takes place by the same rule as for acetophenone.

We performed reactions using the catalyst (*S*)-**1h** under varying reaction conditions of both CBS catalyst and

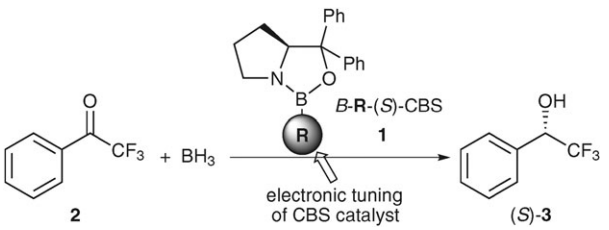

Fig. 2 Electronic tuning of **1** for asymmetric reduction of **2**.

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Table 1 Asymmetric BH_3 reduction of **2**[a,b]

Entry	Oxazaborolidine (R)	Taft's σ^* of R	% ee of **3**
1	**1a** (Me)	0	1.7 (*S*)
2	**1b** (4-Me–C_6H_4)	0.46	76.2 (*S*)
3	**1c** (Ph)	0.6	79.3 (*S*)
4	**1d** (4-F–C_6H_4)	0.63	79.2 (*S*)
5	**1e** (4-CF_3–C_6H_4)	0.96	71.8 (*S*)
6	**1f** (3,5-F_2–C_6H_3)	1.01	80.2 (*S*)
7	**1g** (3,4,5-F_3–C_6H_2)	1.04	80.8 (*S*)
8	**1h** (2,4,6-F_3–C_6H_2)	1.08	84.9 (*S*)
9	**1i** (C_6F_5)	1.5	54.6 (*S*)

[a] The reaction was performed at 30 °C for 1 h. 1 M of ketone solution was added at 20 μL min^{-1} by syringe pump. [b] The conversions were 100% in all reactions, which were confirmed by ^1H NMR.

Table 2 Optimization of asymmetric BH_3 reduction of **2**[a,b]

Entry	CBS **1h**/ mol%	$BH_3{\cdot}SMe_2$/ mol%	Solvent	Temp./ °C	% ee of **3**
1	10	60	THF	0	5 (*S*)
2	10	60	THF	30	85 (*S*)
3	10	60	THF	40	87 (*S*)
4	10	60	THF	50	86 (*S*)
5	10	100	THF	40	90 (*S*)
6	10	120	THF	40	88 (*S*)
7	10	100	Toluene	40	90 (*S*)
8	10	100	CH_2Cl_2	40	88 (*S*)
9	8	100	THF	40	90 (*S*)
10	5	100	THF	40	87 (*S*)

[a] 1 M of ketone solution was added at 20 μL min^{-1} by syringe pump. [b] The conversions were 100% in all reactions, which were confirmed by ^1H NMR.

$BH_3{\cdot}SMe_2$ concentration, solvent, and temperature (Table 2). In the temperature range of 30–50 °C, enantioselectivity slightly changed (entries 2–4), but at lower reaction temperature it decreased significantly (entry 1); this trend is commonly observed in OAB-catalyzed asymmetric BH_3 reductions of ketones.[12] At 1 equiv. of $BH_3{\cdot}SMe_2$, enantioselectivity peaked at 90% ee (entry 5 *vs.* the surrounding 3 and 6). Enantioselectivity was less affected by solvent (entries 5, 7, 8). Regarding CBS concentration, catalyst loading could be reduced from 10% to 8% without loss of enantioselectivity, but further reduction decreased enantioselectivity (entry 9 *vs.* 10). Thus, the choice of optimal conditions permitted highly enantioselective CBS-catalyzed BH_3 reduction of **2**.

Next, we considered the influence of *B*-Ar on enantioselectivity. Although an OAB catalyst with EWGs tended to give products with high enantioselectivity, the data showed no correlation with Taft's σ^* values for the aryl group,[13] causing us to suspect that the steric effect of the fluoro-functional groups of aryl affects enantioselectivity. The mechanism of OAB-catalyzed asymmetric BH_3 reduction is shown in Fig. 3.[3c] Asymmetric induction to **2** occurs at the transition state of hydride transfer (Fig. 3, step C). In our case, Ph was recognized as larger group than CF_3 (Ph > CF_3), similar to the case of reduction of acetophenone (Ph > CH_3)[3c] and contrary to the case of reduction of **2** with catecholborane (Ph < CF_3) as mentioned above.[3c,7,14] Calculations of the transition states **5h** by two-layered ONIOM (MP2/6-31G(d,p):B3LYP/6-31G(d))[15] demonstrated a preference for the formation of (*S*)-**3** (Fig. 4).

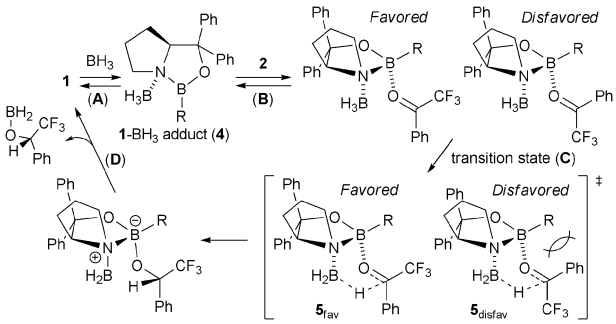

Fig. 3 Typical catalytic cycle of CBS reduction.

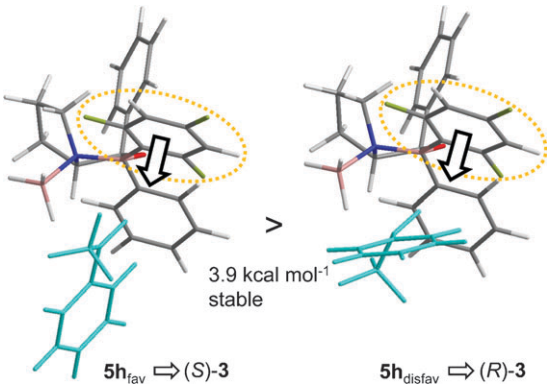

Fig. 4 Transition states **5h** at the hydride transfer step.

Both aryl groups on boron in **5h** oriented their aromatic plane toward the ketonic substrate, suggesting that the steric effect of the substituent on *B*-Ar had negligible influence on the enantioselectivity of the product of reduction of **2**. Therefore, we focused again on electronic effects. Because ketone **2** coordinates to **1**–BH_3 adduct **4** before hydride transfer (Fig. 3, step B), we calculated the π* orbital energy of boron (π^{*B}) in **4**. The corresponding orbitals were found in the LUMO + 4 of **4a** and the LUMO of **4b–4i**. ΔE values were calculated by subtracting the n^O orbital energy of **2** (HOMO − 2 = −7.85 eV) from the π^{*B} orbital energy of **4**, indicating the coordination capability between **2** and **4**. The ΔE values correlated highly with the values of enantioselectivity of **3** (ln[(*S*)-product/(*R*)-product]) (Fig. 5), and the correlation divided into two systems at catalyst **1h** (**4h**). The

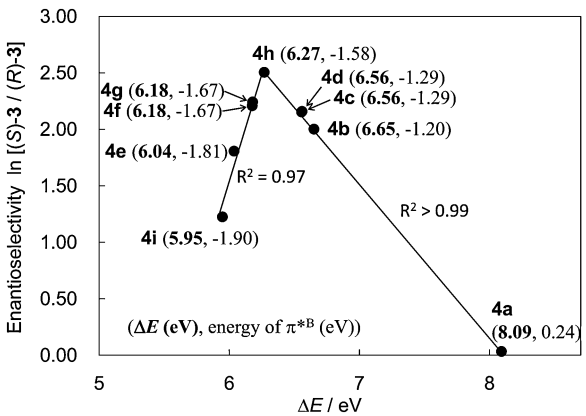

Fig. 5 Correlation between enantioselectivities of **3** and ΔE.

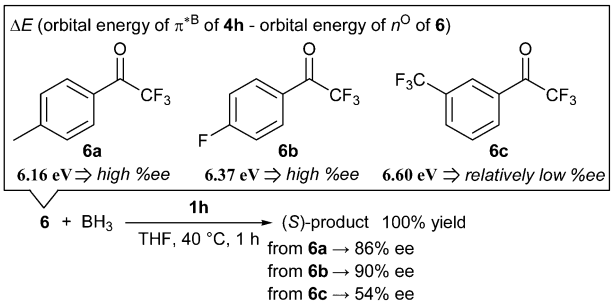

Fig. 6 ΔE values **6**–**4h** for prediction of % ee of BH_3 reduction.

high correlation indicated that the enantioselectivity of the product formed by reduction of **2** was mainly influenced by coordination between **2** and catalyst. When the substituent was *B*-Me (**4a**), coordination between **2** and **4a** was very weak due to the high π^{*B} orbital energy of **4a** (that is, large ΔE), indicating that noncatalytic reduction of **2** with BH_3 occurred dominantly (Table 1, entry 1). When the substituent was changed to *B*-Ar, coordination between **2** and **4** drastically improved (Table 1, entries 2–9), owing to the lower π^{*B} orbital energy (that is, smaller ΔE) of **4** relative to that of **4a**. Although large numbers of fluoro-functional groups tended to decrease ΔE, the order turned back in the case of **4e**, **4f**, **4g** and **4h**. This disorder is because of the mesomeric effect of fluorine's lone pair to the boron atom, particularly at the 2, 4, and 6 positions. The enantioselectivity of product **3** increased with decreasing ΔE values for **4** until **4h** (OAB **1h**) (Fig. 5). However, further decrease in ΔE resulted in a loss of enantioselectivity for **3**, suggesting the generation of an inhibition process. Although one likely reason for the inhibition is dimerization of OAB,[4b] dimer suspect signals could not be observed in ^{19}F NMR analyses of the catalysts **1e**, **1f**, and **1h** in THF at 30 °C. Therefore, we hypothesized that sluggish elimination of the product owing to the strong Lewis acidity of the catalyst inhibited catalyst reproduction (Fig. 3, reaction step D) in the cases of **1e**, **1f**, **1g**, and **1i**. Although the reasons for this phenomenon are not clear, a subtle inhibition process would decrease the enantioselectivity of (*S*)-**3** considerably because of the ease of noncatalytic reduction of **2**.

We obtained the ΔE values between each of the other trifluoroacetophenone analogues **6a–6c** and **4h** by DFT calculations. Each ΔE value between **6a** and **4h** and between **6b** and **4h** was similar to that between **2** and **4h** within the difference of ±0.1 eV; however, the difference of those from the value between **6c** and **4h** was 0.33 eV (Fig. 6). These values indicated that, compared to the product of reduction of **2**, the products of reduction of **6a** and **6b** should have similar enantioselectivity and the product of reduction of **6c** should have lower enantioselectivity.[16] In fact, the products of BH_3 reduction of **6a** and **6b** had similar enantioselectivities (86% and 90% ee, respectively) to the product of reduction of **2** (90% ee) when the catalyst (*S*)-**1h** was used under the same condition, and the product of reduction of **6c** had low enantioselectivity (54% ee) owing to weak coordination between **6c** and **4h**, as indicated by the ΔE value (Fig. 6).

In conclusion, we accomplished highly enantioselective CBS-catalyzed asymmetric BH_3 reduction of **2** by electronic tuning of the catalyst. The enantioselectivity of reaction product (*S*)-**3** is influenced by the coordination capability of **4**. We are now able to predict roughly the enantioselectivities of the products of reduction of **6** from calculated ΔE values, although at present these predictions can be applied exclusively to trifluoroacetophenone analogues. Such electronic control of CBS catalysis should be effective for other highly reactive substrates if the relationship between catalyst and substrate is well designed.

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16 The correlations in Fig. 5 are not applied to the results of reduction of **6** as it is, because EWG in phenyl group accelerates non-catalytic BH_3 reduction, particularly, in **6c**. See ref. 8*b*.

