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# The enantioselective reduction of 2′-fluoroacetophenone utilizing a simplified CBS-reduction procedure

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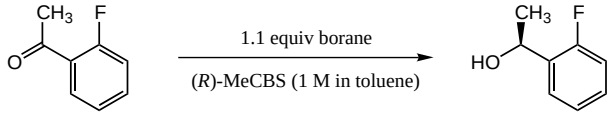
**Abstract**—We have developed a practical, non-enzymatic, catalytic process for the enantioselective reduction of 2′-fluoroacetophenone. A number of catalysts were screened for the oxazaborolidine-type reduction of this ketone to obtain an optimized system. We have shown that the simplest procedure uses the catalyst formed in situ from (*S*)-α,α-diphenyl-2-pyrrolidinemethanol ((*S*)-**2**) and borane–diethylaniline. 

In the course of developing a process for the synthesis of (*S*)-2-fluoro-α-methylbenzenemethanol **1** we needed to evaluate chiral reduction methods which would generate the product in ≥98% ee. Literature examples indicated that the most efficient reduction methods were typically enzymatic and formed the product with very high ee (99–100%).[1] We had in hand a non-enzymatic, stoichiometric reduction method that gave the product in 98% ee,[2] but for processing reasons, we desired a non-enzymatic, *catalytic* method. We therefore set out to evaluate catalytic reduction methods based on the oxazaborolidine system, which on first-pass had yielded the product with 93% ee in the presence of (*R*)-MeCBS **3b** and a stoichiometric reductant (Scheme 1).[3] As we would need to produce **1** on a large scale, the process safety, as well as the selectivity of the reduction, would need to be evaluated.

It was initially necessary to determine the optimal oxazaborolidine catalyst for this reduction. A search of the literature indicated that preparing the MeCBS reagent (Scheme 2, **3b**) in situ can be fraught with problems.[4] A variety of intermediates are possible which can result in variable selectivity depending on the method used for catalyst generation.[5]

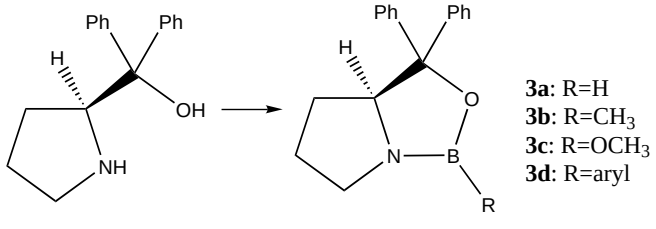
Additionally, the substituent on boron can play a dramatic role in governing the selectivity and stability of the catalyst system. The most common substituents on boron are R = H, alkyl, or aryl (Scheme 2). Catalyst **3a**, which can also be formed in situ, is known to be more sensitive to air and moisture than the corresponding R = Me compound (**3b**); both can be difficult to prepare consistently. This difficulty has led to many studies which compared catalysts with various R-groups, often arriving at different conclusions as to which substituent is optimal.[6–8] The R = H catalyst provides, in many cases, superior enantioselectivities, but the difficulty in preparing it consistently is a problem.[6] The temperature-dependency of the selectivity has also been the topic of several studies.[8,9]




(*S*)-**1**

93% ee

**Scheme 1.** Unoptimized MeCBS reduction leading to (*S*)-**1**.




(*S*)-**2** (*S*)-**3a-d**

**Scheme 2.** Some oxazaborolidine catalysts.

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While the choice of catalyst is obviously important with respect to the enantioselectivity of the reaction, the choice of a suitable stoichiometric reductant is critical from a process safety perspective. We chose to use borane–diethylaniline complex (DEANB) as our stoichiometric reductant as this is a stable, concentrated borane reducing agent,[6] which does not have the undesirable properties associated with other borane reagents, such as those complexed with ethers or sulfides. Some of the drawbacks commonly noted with respect to the ether and sulfide complexes are thermal instability, odor, and low concentration. While we were completing our process studies on the generation of **1** using oxazaborolidines and DEANB, a paper was published,[10] which nicely reinforced our choice of stoichiometric reductant in large-scale pharmaceutical processing. The results of our studies are disclosed below.

Our optimization studies included the use of the commercially available MeCBS reagent **3b**[11] as well as catalysts which were generated in situ **3a** and **3c**.[7,12] We used DEANB as our primary stoichiometric reductant, and optimized a number of variables such as solvent, concentration, temperature, catalyst loading, rate of ketone addition, and equivalents of borane. We performed the optimizations using the Surveyor™ parallel reactor system[13] and statistically designed experiments.[14] The major response used for analysis was the ee of the product.[15] Selected results from these studies are shown in Table 1.

A significant effect of temperature on the selectivity was noted for this substrate when using catalysts **3b** and **3c** (Table 1, compare entries 1 and 2; entries 3 and 4). The rate of addition of the ketone is critical in obtaining high ee. When the ketone is added over 30 min, the ee is fairly high, but when the addition rate is increased the ee decreases significantly. This effect is exacerbated at lower temperatures (Table 1, compare entries 4 and 5).

When catalyst **3a** is formed in situ, the ee is at least as good, if not better, than that observed with catalysts **3b** and **3c** (Table 1, compare entry 6 with entries 1 and 3). The ee drops only slightly when the loading of **3a** is decreased to 1 mol% (Table 1, compare entries 6 and 7). This is quite a promising result, as the use of **3a** could greatly decrease the cost and complexity of the catalyst system. Although it is somewhat surprising that **3a** is so effective, several possible explanations for this result can be found in the literature.

The use of a stoichiometric amount of amine has been shown to have a positive effect on the enantioselectivity of the reaction;[16] in our case we use a stoichiometric amount of diethylaniline from the borane reagent. The positive effect of the amine on the ee of the reaction is also indicated in our studies using $BH_3$–THF (Table 1, compare entries 8 and 9). In addition, the higher temperatures utilized here may facilitate faster formation and regeneration of the active catalyst. Also at higher temperatures the reduction occurs more quickly, so faster rates of addition can be tolerated.[5]

Therefore, the reduction of 2′-fluoroacetophenone to generate **1** occurs with high enantioselectivity with three different catalysts (Table 1, entries 1, 3, and 6),[17] although we would consider the use of catalyst **3a** the best result. With this catalyst (generated in situ) we could synthesize **1** in high ee (97.8%), using only one catalyst additive ((*S*)-**2**), with a stable, safe borane source (DEANB),[18] and requiring a non-chromatographic workup to generate product of high purity.[19] This is in contrast to many of the published reports which suggest that the ee is highly dependent on the catalyst structure and that the preparation of catalysts in situ is difficult to perform consistently without careful controls. All of the reactions shown in Table 1 were performed with reagent grade, unpurified materials. No additional drying steps were performed for any of these materials, which also suggests that there is no detrimental effect of trace water on the in situ catalyst formation.

In conclusion, our data indicate that for the preparation of **1**, several catalyst systems are viable, and the reaction does not appear to be very sensitive to trace impurities, as no special effort was made to eliminate them from our standard reagents. This provides, along with other literature examples, further data to show

**Table 1.** Summary of results for the generation of **1**[a]

| Entry | Catalyst | Temp. (°C) | % ee | Config. **1** |
|---|---|---|---|---|
| 1 | (*R*)-**3b** | 45 | 96.9 | *S* |
| 2 | (*R*)-**3b** | 20 | 92.0 | *S* |
| 3 | (*S*)-**3c** | 40 | 97.6 | *R* |
| 4 | (*S*)-**3c** | 20 | 92.2 | *R* |
| 5 | (*S*)-**3c** | 20[b] | 85.9 | *R* |
| 6 | (*S*)-**3a** | 45 | 97.8 | *R* |
| 7 | (*S*)-**3a**[c] | 45 | 96.8 | *R* |
| 8 | (*S*)-**3a**, $BH_3$–THF, 1 equiv. diethylaniline | 45 | 96.8 | *R* |
| 9 | (*S*)-**3a**, $BH_3$–THF | 45 | 91.6 | *R* |

[a] Unless otherwise noted, all reactions were completed with 1.1 equiv. of DEANB, 30 min addition time for the ketone, 0.07 M 2′-fluoroacetophenone in *tert*-BuOMe and 8 mol% of catalyst. All reactions were complete at the end of the ketone addition.

[b] The reaction took 30 min to reach complete conversion after the addition of ketone was complete (5 min).

[c] 1 mol% of catalyst was used.

that the oxazaborolidine-type reduction systems are an efficient method for generating the desired enantiomerically pure product. In this case, **3a** is the simplest and most effective catalyst. In short, we recommend the in situ formation of the catalyst using **2** and DEANB as the method of choice when reductions of this type are to be employed.

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10. Wilkinson, H. S.; Tanoury, G. J.; Walk, S. A.; Senanayake, C. H. *Org. Process Res. Dev.* **2002**, *6*, 146–148. The catalyst used in this study was prepared from enantiomerically pure *cis*-1-amino-2-indanol, not **2**.
11. Available in bulk from Aldrich Chemical Company and Callery Chemical Company.
12. While (*R*)-MeCBS was readily available, (*R*)-**2** was more expensive than (*S*)-**2** on a small scale. Therefore, (*S*)-**2** was used for the in situ generation of catalysts. This leads to (*R*)-**1**, as would be expected.
13. Surveyor is a product of Argonaut Technologies.
14. Using statistically designed experiments (DoE) these factors were evaluated in 30 runs. Typical procedures are as follows:
    **3b**: DEANB (0.66–1.1 equiv.) was mixed with **3b** (1 M in toluene, 0.02–0.15 equiv.) and solvent (3.5 mL). The solution was warmed to the reaction temperature (20–55°C), and the ketone solution (1.0 equiv. in 7 mL of solvent) was added over 5–30 min while maintaining the reaction at the desired temperature.
    **3a**: (*S*)-**2** (0.075 equiv.) was dissolved in *tert*-BuOMe (3.5 mL) and DEANB (1.1–2.0 equiv.). The solution was warmed to the reaction temperature (20–45°C), and the ketone (1.0 equiv.) was added as a solution in *tert*-BuOMe (7 mL) over 5–30 min, while maintaining the reaction at the desired temperature.
    **3c**: Trimethyl borate (0.09 equiv.) was mixed with (*S*)-**2** (0.075 equiv.) in *tert*-BuOMe (3.5 mL). This solution was stirred at room temperature, and DEANB (1.1–2.0 equiv.) was added after a set amount of time. The solution was warmed to the reaction temperature (20–45°C), and the ketone (1.0 equiv.) was added as a solution in *tert*-BuOMe (7 mL) over 5–30 min, while maintaining the reaction at the desired temperature.
    The progress of each reaction was followed by HPLC after the ketone addition was complete.
15. Enantiomeric excess was determined by HPLC (Daicel Chiralpak AD column, 0.46 cm×25 cm, 5 μL injection, 40°C, 210 nm, 99:1 hexane:ethanol, 1 mL/min, 16 min run, (*R*) 10.06 min, (*S*) 11.04 min).
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17. Using catalyst (*R*)-**3b**, the reaction was performed on 150 g of 2′-fluoroacetophenone, generating **1** with 98% ee and in 96% yield. The stereochemical assignment of this product was confirmed by comparison of the specific rotation with published values (Ref. 1).
18. The optimum conditions call for mixing (*S*)-**2** (2.0 g, 0.075 equiv.), *tert*-BuOMe (30.3 mL), and DEANB (22.5 mL, 1.2 equiv.). This solution was warmed to 45°C, and a solution of ketone (14.5 g, 1.0 equiv.) in *tert*-BuOMe (60.6 mL) was added over 0.75 h, while maintaining the reaction temperature at 45°C. After the ketone addition was complete, analysis indicated complete conversion to **1** (97.8% ee).
19. Standard workup: For a 1.1 mol reaction, the reaction solution was cooled to 0–10°C under a rapid flow of nitrogen and methanol (702 mL) added over about 20 min while the reaction temperature was maintained at <10°C. *Caution*: *the quench is exothermic and generates $H_2$ gas, so care should be taken when performing this operation.* Once the addition was complete, the solution was warmed to room temperature and stirred for at least 0.5 h. The solvents were removed at 65°C and 500 mbar to azeotropically distill the methanol (and toluene if it is present) as well as to further quench and remove the boron-containing reagents.
    The resulting residue was diluted with *tert*-BuOMe (935 mL) and washed with 1N aqueous HCl (935 mL). The organic layer was removed and set aside, while the aqueous layer was back-extracted with *tert*-BuOMe (935 mL). The organic layers were combined and washed with 1N HCl (935 mL), water (935 mL) and 10% brine (935 mL). The organic solution was dried over $MgSO_4$ (70 g), the solution was filtered, and the solvents removed resulting in **1** as a colorless, free-flowing oil, typically of >98% purity.