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An Improved Method for Chiral Oxazaborolidine-catalyzed Reduction of 4-Chromanone Analogs and MK-0499[1]

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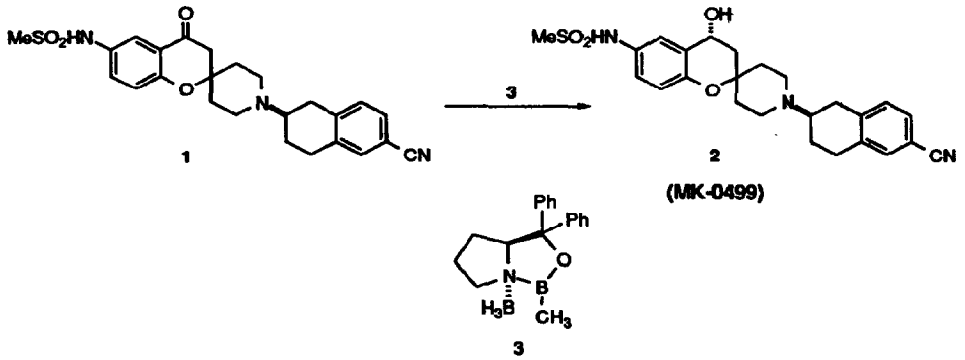
Abstract: *Addition of isopropanol to the stoichiometric reduction of ketones 4 - 8 using oxazaborolidine-borane complex 3 or the oxazaborolidine-catalyzed reduction of 4-chromanone analogs (1, 7 - 9) enhances the enantioselectivity of the reduction.*

The antiarrhythmic drug candidate **2** (MK-0499)[2] is a potent potassium channel blocker for treatment of life-threatening arrhythmia and the prevention of sudden cardiac death. It is currently undergoing intensive clinical trials. The preparation of **2** involves a multi-step synthesis. One of the key steps requires an enantioselective reduction of ketone **1** to chiral alcohol **2** shown in Scheme I. Although an excellent enantioselectivity (>99% ee) has been achieved by using stoichiometric amounts of oxazaborolidine-borane complex (OAB-BH_3) **3** as reported previously,[2,3] a catalytic reduction of ketone **1** to alcohol **2** was highly desirable for large scale preparation of this drug candidate.[4,5] In this letter we report our development of a practical method for catalytic reduction of ketone **1** to alcohol **2** using catalyst **3**.

Scheme I



A couple of unique structural features of ketone 1 are worth noting: (a) the 4-chromanone with a spiro-fused ring system; (b) the tertiary amine within the piperidine ring capable of complexing with borane.[6] Based on the conventional methods for OAB-catalyzed reduction, three procedures were examined.[5,7,8] Unfortunately, the enantioselectivities of the reduction of ketone 1 to alcohol 2 were disappointing (88-94% ee). In addition, recrystallization did not upgrade the % ee of alcohol 2 without significant yield loss (20-30%).

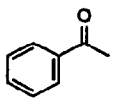
Previous results from our laboratory indicated that two hydrides can be transferred from the OAB-BH_3.[5] Earlier work also indicated that the enantioselectivity of the second hydride transfer was lower than the first.[3a] In addition, we observed that the addition of triethylamine (Et_3N) improved the enantioselectivity of the reduction by possibly intercepting a reactive intermediate prior to the second hydride transfer.[3a] However, Et_3N can not be used to enhance the enantioselectivity of *a catalytic process*, because it forms a tight Et_3N-BH_3 complex.[3a,6]

In searching for an alternative additive which would intercept the reactive intermediates without inhibiting the catalytic cycle, we discovered that some alcohols, e.g. i-PrOH, efficiently enhanced the enantioselectivity of the reduction. When the enantioselective reductions were carried out stoichiometrically, similarly to the Et_3N cases, enhancements of the enantioselectivies were observed. For example, Table I summarizes the results when 4-chromanone (6) was used as a model ketone.

Table I. The Effect of Additives on the Stoichiometric Reduction of 4-Chromanone[9]

Additives	NONE	EtOH	i-PrOH	t-BuOH	Et_3N[3a]
% ee	93.0	94.3	98.3	98.2	99.3

An enhancement of the enantioselectivity was also demonstrated in the reduction of model ketones 4 - 8 when i-PrOH was used as an additive (Table II).



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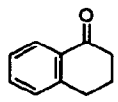

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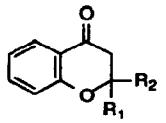
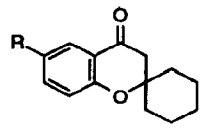


6, $R_1 = R_2 = H$
7, $R_1 = R_2 = Me$



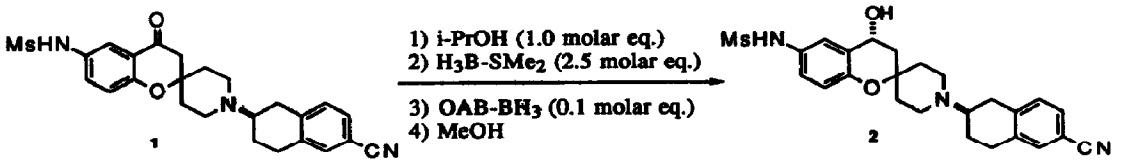
8, R = H
9, R = NHMs

Table II. The Effect of i-PrOH on the Stoichiometric Reduction of Model Ketones[9]

Ketones	4	5	6	7	8
% ee[9a]	93	90	93	93	91
% ee[9b]	94.9	98.1	98.3	99.3	99.4

To extend the i-PrOH effect to the *catalytic process*, addition of i-PrOH to the OAB-catalyzed reduction of ketone 1 was examined. Indeed, the enantioselectivity was improved from 92% to 98% ee (Scheme II).

Scheme II



A typical procedure: the solution of ketone **1** in methylene chloride is treated with i-PrOH (1.0 mole) and borane methyl sulfide (BMS, 2.5 moles) at -20 °C for 30 min. (at this point the amine borane complex **1**-BH_3 is formed, but no racemic reduction by BMS occurs)[10] followed by addition of catalyst **3** (0.1 mole). The mixture is slowly warmed to 15 °C over 45 min. and kept for 30 min. at 15 °C for the completion of the reduction (monitored by HPLC). Methanol is used to quench the reaction at 15 °C and low boiling by-products $(MeO)_3B$, Me_2S and methylene chloride are removed by atmospheric distillation. Heating the mixture to 65 °C is required in order to break the amine-borane complex (**2**-BH_3). The reaction yield is >90% and the product shows 98% ee (determined by HPLC assay of the Mosher esters[11]). Recrystallization of the product affords pure **2** in 92% yield with 99% ee.

Various alcohols were also examined for this reaction, and the results showed that the reduction with the addition of t-BuOH, n-PrOH, EtOH and MeOH provided the alcohol **2** in 97%, 96%, 96% and 80% ee, respectively. To study the generality of this i-PrOH modified OAB-catalyzed enantioselective reduction procedure we reduced ketones **5** - **9** under the same conditions (Table III).

Table III. The Effect of i-PrOH on the Catalytic Reduction of Model Ketones[12]

Ketones	5	6	7	8	9	1
% ee[9a]	90	90	88	89	88	92
% ee[9b]	90	92	95	94	94	98

Interestingly, our results in Table III show that the i-PrOH modified catalytic procedure does substantially enhance the enantioselectivity of 2-substituted 4-chromanones (entries **1**, **7** - **9**). However, adding i-PrOH under the reaction conditions described above had little or no effect on simple α-tetralone and unsubstituted 4-chromanone. At this time, the exact mechanism of the i-PrOH modified OAB-catalyzed reduction is not clear. Studies to elucidate the mechanism of this i-PrOH effect are ongoing.[13]

In summary, a new highly efficient enantioselective process for reduction of 2-substituted 4-chromanones was developed. This i-PrOH modified OAB-catalyzed reduction was demonstrated for large scale preparation of chiral alcohol **2** with an excellent enantioselectivity.

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(9) All reductions were run by the addition of OAB-BH_3 (0.6-0.7 or 1.2-1.3 mole equivalent) to a CH_2Cl_2 solution of the ketone or the ketone with the addition of 2.0 mole equivalents of alcohol at -15 °C. The chiral alcohols were purified on a silica gel column and characterized by NMR, and enantioselectivities were determined on a chiral HPLC column. (a) without the addition of i-PrOH; (b) with the addition of i-PrOH.

(10) An NMR study indicates that i-PrOH reacts with H_3B-SMe_2 slowly at -20 °C and the free i-PrOH (15-20%) remained after 60 min. at -20 °C.

(11) Dale, J.A.; Mosher, H.S. *J. Am. Chem. Soc.* 1973, *95*, 512.

(12) All of the examples in Table III were reduced under the same conditions with or without added i-PrOH in order to investigate the effect of i-PrOH. While **5** can be reduced in 99% ee by a slow addition technique, our substrate **1** does not provide the desired enantioselectivity under those conditions (ref. 5).

(13) Several intermediates derived from the reaction of OAB-BH_3 with the ketone have been detected by NMR studies at low temperature. The structures and properties of the intermediates will be published elsewhere.

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