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Process for preparing Ezetimibe intermediate by an acid enhanced chemo- and enantioselective CBS catalyzed ketone reduction☆

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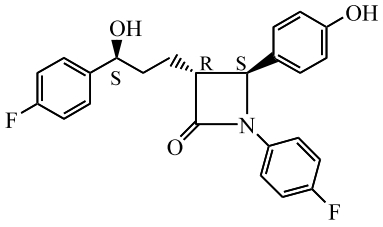
Abstract—The *S* alcohol in the benzylic position of compound **2**, a key feature of a novel cholesterol lowering agent Ezetimibe, was introduced by the (*R*)-MeCBS catalyzed asymmetric carbonyl reduction of ketone **1** using borane tetrahydrofuran complex (BTHF) as the reducing agent. The chemo- and enantioselectivity was dramatically enhanced by using an acid as a scavenger of the stabilizer sodium borohydride present in the commercially supplied pure BTHF. The effect of the critical reaction parameters such as addition mode of reagent, temperature, acids as well as water content on the selectivity has been examined. This reaction has been successfully applied in the commercial process for the preparation of the key intermediate **2** for Ezetimibe.

Ezetimibe (SCH 58235, 1-(4-fluorophenyl)-3(*R*)-[3-(4-fluorophenyl)-3(*S*)-hydroxypropyl]-4(*S*)-(4-hydroxyphenyl)-2-azetidinone) is a novel and potent agent that selectively inhibits cholesterol absorption across the intestinal wall. It was reported from clinical studies that Ezetimibe significantly decreased plasma LDL cholesterol levels and increased plasma HDL levels with an excellent tolerability profile.[2] More interestingly, it has been demonstrated that Ezetimibe has additive effects with the statins such as simvastatin. This combination has been shown to improve LDL reduction to 52% as compared to 35% with simvastatin alone.[3] The metabolism-based discovery[4] of this compound with a novel mechanism for lowering cholesterol has stimulated much interest in synthetic approaches to efficiently assemble the molecule.[5] The reported syntheses focused on the construction of the azetidinone ring first followed by introduction of the benzylic chiral hydroxyl group. A more convergent approach has been developed to synthesize Ezetimibe by preparing the (*S*) hydroxy side chain before the ring construction.[6] We wish to report an acid enhanced CBS catalyzed chemo- and enantioselective synthesis of a key (*S*) hydroxy Ezetimibe intermediate **2**.



Ezetimibe (SCH 58235)

Reduction of carbonyl compounds with chiral oxazaborolidine catalysts has been demonstrated as a powerful method for the synthesis of chiral alcohols from prochiral ketones.[7] A variety of borane reagents have been employed for this reaction including borane tetrahydrofuran complex (BTHF), borane dimethylsulfide complex (BMS), borane 1,4-thioxane, borane diethylaniline,[8] borane *N*-ethyl-*N*-isopropylaniline,[9] *N*-borane phenylamine,[10] catecholborane, and in situ generated borane.[11] BMS is generally considered to be a more stable and less reactive reagent than BTHF, and it has been widely used in CBS catalyzed ketone reductions. However, the use of BMS complex leads to environmental concerns due to release of methylsulfide. Therefore, BTHF has an advantage over BMS for industrial applications.

Keywords: Ezetimibe; *R*-MeCBS; asymmetric ketone reduction.

☆ This chemistry was disclosed in our patent application which was filed on March 28, 2001. See Ref. 1.

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Reduction of ketone **1** with BMS in the presence of (*R*)-MeCBS provided (*S*)-chiral alcohol **2** with excellent enantioselectivity (>98% de, vs **3**) in greater than 95% yield. The addition sequence of reagents was to add **1** slowly into a premixed solution of BMS and catalyst. Due to the increased reactivity of BTHF over BMS, simple replacement of BMS with BTHF in the reduction generated a substantial amount (>30%) of overreduction of the amide bond to give the diol **4**, identified by HPLC/MS analysis. Attempts to separate the diol **4** from the major product **2** were unsuccessful due to its instability. Instead, (*S*)-(+)-4-phenyl-2-oxazolidinone was isolated as a by-product of the decomposition. The enantioselectivity was comparable with the BMS reaction (>95% de). Attempts to overcome the chemoselectivity problem by introduction of additives[12] such as isopropanol and triethylamine, pyridine, and 2,6-lutidine were unsuccessful. When triethylamine (0.25 equiv.) was used as an additive, the reaction proceeded with good de (93%) and the overreduced by-product was less than 5%. However, the reaction was not complete when all of **1** was charged slowly, and additional BTHF was required to push the reduction to completion. These results implied that the complex of triethylamine with borane formed in situ was not reactive enough for the reduction. This was confirmed by carrying out the reaction with commercially available borane triethylamine complex. The results also hinted that change of the addition mode might offer an advantage to resolve the chemoselectivity issue since limiting the BTHF reagent should allow the reaction with the more reactive ketone function in the presence of the amide bond. When the reaction was executed by adding about 0.6 equiv. of BTHF to a solution of **1** in the presence of 3% (*R*)-MeCBS catalyst in THF, the chemoselectivity was indeed controlled to less than 1% diol and the reaction gave a near quantitative yield with ~95% de (Scheme 1). It is critical to divide the BTHF addition into two portions. The reaction progress was monitored by HPLC analysis when about 85% of the calculated amount of reagent was charged. The rest of the BTHF was added based on the reaction completion to minimize overreduction to diol **4**.

The temperature effects on the enantioselectivity of the reduction were studied and the results are summarized in Table 1. As reported in the literature,[13] the enantioselectivity decreases with decreasing temperature. The reduction of **1** gave the best enantioselectivity at a temperature of about 25°C. It should be noted that the reaction can be conducted over a wide temperature range such as −10 to 35°C to produce the chiral alcohol with acceptable selectivity since the corresponding products from the minor diastereomer **3** are largely removed during the subsequent purification steps.

Table 1. Temperature effects on the enantioselectivity

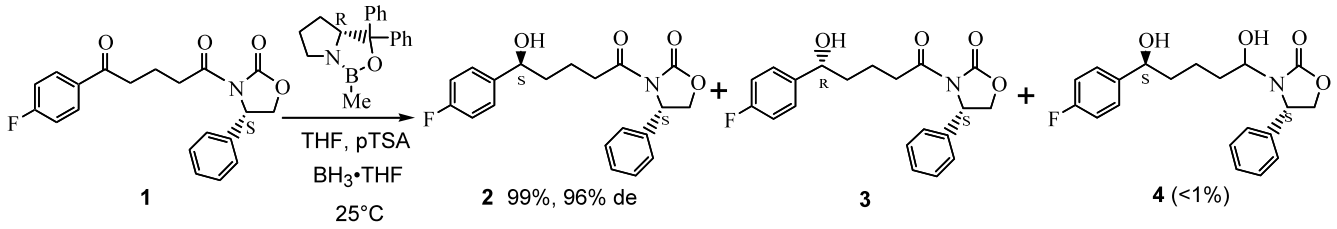
Entry	Temperature	Enantioselectivity (% de)
1	−11	92.5
2	0	93.3
3	10	93.9
4	18	95.2
5	25	96.2
6	35	94.5

Due to the sensitivity of the *R*-MeCBS catalyst to moisture, it is critical to keep the reaction mixture free of water. For example, when the water content was 0.3% by KF analysis, the reaction only yielded the chiral alcohol **2** in 70% de compared to 95% de under the dry conditions (~0.02% by KF). Decomposition of the catalyst with water would produce diphenylprolinol. Although *R*-diphenylprolinol itself was reported to catalyze ketone reduction to give high enantioselectivity, it only provided moderate de (~70%) under our reaction conditions for the reduction of **1** to **2**. To ensure dry conditions, the solution of **1** in THF was concentrated to the water content of below 0.02% by KF analysis.

The results described above were all from the reactions using BTHF from Aldrich. Since Aldrich was not the primary commercial supplier for BTHF, it was desirable to look for alternative sources for both the price and availability of this reagent. Callery Chemical is the primary supplier for borane tetrahydrofuran complex. To our surprise the reduction of **1** gave a much inferior selectivity when the BTHF from Callery Chemical was used. To understand the reasons for the lower selectivity with borane tetrahydrofuran complex purchased from Callery, NMR studies on the BH_3·THF were initiated. Analysis of the proton NMR spectrum clearly indicated that about 3–5% of borane 1-butanol complex was present in the Aldrich samples which was absent in the other samples. Boron NMR suggested that the complex was a mixture of di-butoxyborane (major) and mono-butoxyborane. Clearly the formation of those compounds was from the complexation of borane with 1-butanol which was generated by the reduction of tetrahydrofuran with BH_3·THF. The di-butoxyborane prepared by reaction of 1-butanol and borane was mixed with the Callery BTHF complex and used for the reduction. However the results indicated that the butoxyborane had no effect on the selectivity.

Careful analysis of the boron NMR also indicated that some other minor boron species were present in the Aldrich borane. One possibility could be BF_3 etherate since it might be used in the generation of diborane gas. With this in mind, we conducted a systematic study on the effect of acid additives on the selectivity of the reduction.

When the reduction was conducted with Callery borane mixing with 1 mol% of BF_3·OEt_2[14] the selectivity significantly enhanced from about 87% de to about 94% de. This result supported the hypothesis of a trace amount of BF_3·OEt_2 present in the Aldrich borane which actually assisted the chiral reduction to achieve higher selectivity. The butoxyborane species present in the Aldrich borane, but absent in the Callery borane, could now be easily understood for the acid destroyed



Scheme 1. *R*-MeCBS catalyzed reduction of **1**.

Table 2. Acid additive effects on the enantioselectivity

Entry	BH_3·THF source	Acid (mol% to BH_3)	Selectivity	
			SS **2**/*SR* **3**	% de
1	Callery	None	93.7/6.3	87.4
2	Aldrich	None	96.3/3.7	92.6
3	Callery	BF_3·OEt_2 (1%)	96.9/3.1	93.8
4	Callery	BF_3·OEt_2 (2.5%)	96.7/3.3	93.4
5	Callery	BF_3·OEt_2 (5%)	97.5/2.5	95.0
6	Callery	BF_3·OEt_2 (10%)	96.7/3.3	93.5
7	Callery	BCl_3 (5%)	95.3/4.7	90.6
8	Callery	pTSA (5%)	96.5/3.5	93.0
9	Callery	TFA (5%)	95.9/4.1	91.8
10	Callery	MSA (5%)	96.0/4.0	92.0
11	Callery	CSA (5%)	96.6/3.4	93.2

The product selectivity was calculated from chiral HPLC analysis (Chiralcel OD column, 30% EtOH in hexane as mobile phase with a flow rate of about 0.7 mL/min, an UV detector at 215 nm).

Table 3. Effects of *R*-MeCBS loading on product % de

R-MeCBS (%)	KF (ppm)	de (%)	Diol (**4**) (%)
1	54	93.1	0.97
2	50	95.1	0.25
3	67	95.3	0.89

All experiments were carried out with addition of 3% pTSA to compound **1** in THF. The solution was subsequently dried via distillation before the addition of *R*-MeCBS.

the stabilizer ($NaBH_4$). It was obvious that the stabilizer, $NaBH_4$, participated in the reduction of **1**, which resulted in the racemic **2**. The overall result would reduce the selectivity (% de). Different acids were screened for this reduction. The results are summarized in Table 2.

It is clear from the above results that the various acid additives can significantly enhance the enantioselectivity for the reduction of **1** to **2**. It is interesting to note that the $NaBH_4$ present in the BTHF has not only detrimental effects on the enantioselectivity but also on the chemoselectivity. Experiments were carried out with addition of an extra 2.7% $NaBH_4$ into the reaction to test the effect on the overreduction. There was greater than 9% of diol **4** observed with extra $NaBH_4$ while less than 3% was detected in the control experiment. It was no surprise that the selectivities were dramatically different (52% de with $NaBH_4$ vs 87% de by the control). In a separate experiment with 3% pTSA added to the reaction mixture, the % de was enhanced to greater than 95% while the overreduction of product was held under 0.5%. The results demonstrated clearly that the reaction with pTSA was much cleaner than without pTSA. The process with the addition of $NaBH_4$ scavenger (an acid) is robust and the reaction parameters are easily controlled. When a Lewis acid such as BF_3·OEt_2 is used, the Lewis acid reacts directly with $NaBH_4$ to form BH_3. However, when a protic acid such as pTSA is employed, the structures of the active species which destroys $NaBH_4$ is not very clear and might be an adduct of the acid and BH_3. Further studies are needed to understand the reaction pathway in detail.

The effect of the *R*-MeCBS catalyst loading on the enantioselectivity was also tested in order to develop a most cost effective commercial process. The results are tabulated in Table 3. The results indicated that the catalyst loading has a less profound effect on the selectivity than the other parameters described above.

In summary, an efficient *R*-MeCBS catalyzed ketone reduction protocol has been successfully applied in the process for preparation of Ezetimibe intermediate **2**. An acid additive such as pTSA has dramatic effects on both the chemo- and enantioselectivities. The robust process has been scaled up to multikilogram levels.

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