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# Highly Enantioselective Oxazaborolidine-Catalyzed Reduction of 1,3-Dicarbonyl Compounds: Role of the Additive Diethylaniline

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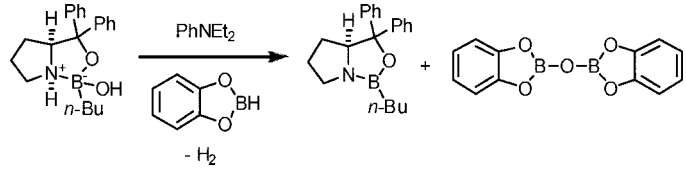
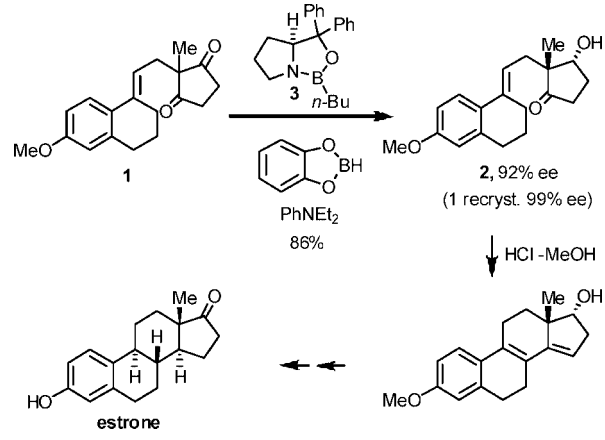
## ABSTRACT




**The oxazaborolidine-catalyzed reduction of 2,2-disubstituted cycloalkan-1,3-diones or hindered 2,2-disubstituted cyclic ketones using catecholborane as reductant proceeds with greater enantioselectivity when *N,N*-diethylaniline is added. It has now been shown that the effect of this additive is to catalyze the conversion of a harmful minor impurity in catalyst preparations to the active catalyst.**

We recently described a practical and short enantioselective synthetic route to estrone from the Torgov diketone (**1**) based on the highly enantioselective and diastereoselective reduction of **1** to the $\beta$-hydroxy ketone **2** with a catalytic amount of the chiral oxazaborolidine **3** and stoichiometric catecholborane using *N,N*-diethylaniline as an additive (Scheme 1).[1] The use of this additive had a dramatic and beneficial effect on the enantioselectivity (96: 4) and also accelerated the reaction. Remarkably also, in the absence of *N,N*-diethylaniline the *opposite* enantiomer predominated somewhat (by between 60: 40 and 75: 25 in various experiments).[1] Our initial surmise was that the additive opened up the possibility of an alternative mechanistic pathway that is distinctly different from the normal CBS pathway.[2] This paper reports on a study to ascertain the basis for the salutary effect of *N,N*-diethylaniline on the CBS reduction of 1,3-dicarbonyl compounds, which was found to be quite general for a whole series of cyclic 1,3-dicarbonyl substrates.[1]

**Scheme 1.** Practical and Short Enantioselective Synthetic Route to Estrone from Torgov Diketone




The reduction of achiral cyclic 1,3-dicarbonyl compounds by a chiral reagent is complicated by the fact that the two carbonyl groups are diastereotopic and not equivalent. As a

(1) Yeung, Y.-Y.; Chein, R.-J.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 10346–10347.

(2) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012.

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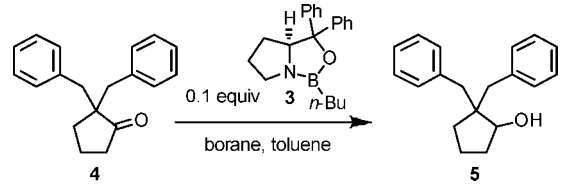
**Table 1.** Effect of Borane Source on the Oxazaborolidine-Catalyzed Reduction of 2,2-Dibenzylcyclopentanone

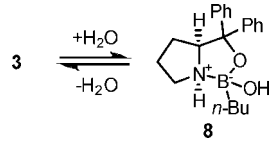



| entry[a] | borane (equiv) | $T$ (°C) | time | conversion (%)[b] | ee (%)[c] | $[\alpha]_D$[d] | config [e] |
|---|---|---|---|---|---|---|---|
| 1 | $BH_3$-THF (1.0) | 23 | 2 h | 100 | 95 | −35.2 | R |
| 2 | $BH_3$-$Me_2S$ (1.0) | 23 | 2 h | 100 | 97 | −36.0 | R |
| 3 | $BH_3$−$PhNEt_2$ (1.0) | 23 | 2 h | 100 | 92 | −34.6 | R |
| 4 | catecholborane (1.8) | −50 | 3 h | 73 | −62 | +23.3 | S |
| 5 | catecholborane (1.8) + $PhNEt_2$ (0.5) | −50 | 3 h | 54 | 92 | −34.5 | R |

[a] In each case the catalyst was prepared from (*S*)-1,1-diphenylpyrrolidinemethanol and *n*-$BuB(OH)_2$ by heating in toluene at reflux in a Dean−Stark apparatus containing 4 Å molecular sieves. [b] Conversion measured by $^1$H NMR analysis. [c] Determined by HPLC analysis using a Chiracel OD column. [d] Rotation determined in $CHCl_3$ solution ($c$ = 1.0). [e] Absolute configuration of **5** was established by X-ray diffraction analysis (see Supporting Information).

result, in the case of Torgov diketone **1** four different compounds can be produced by reduction, since there are enantiomeric forms of the hydroxy/methyl *cis* or *trans* diastereomers.

**Scheme 2**

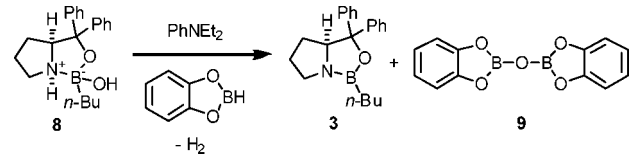



To study the question of whether *N*,*N*-diethylaniline causes a change in the face selectivity of reduction catalyzed by oxazaborolidine **3**, we examined the reduction of a simple monoketone acetophenone. With this substrate in toluene at −50 °C with catalyst **3** and catecholborane as stoichiometric reductant, the product was (*R*)-1-phenylethanol, the expected product of the regular CBS pathway.[2] The same was true with the somewhat less reactive 4-methoxyacetophenone and *tert*-butyl phenyl ketone as substrates under these conditions. In all of these experiments the catalyst **3** was prepared from *n*-butylboronic acid and (*S*)-1,1-diphenylpyrrolidinemethanol in toluene at reflux in a Dean−Stark apparatus containing 4 Å molecular sieves. In contrast, when the reduction was carried out with the more hindered substrate 2,2-dibenzylcyclopentanone (**4**), quite divergent results were obtained with catecholborane in toluene at −50 °C in the presence or absence of *N*,*N*-diethylaniline, as summarized in Table 1, entries 4 and 5. For each of these experiments the reduction was incomplete after a reaction time of 3 h, consistent with the relative unreactivity of this hindered ketone. The dramatic change in the absolute stereochemical course of the reduction with added *N*,*N*-diethylaniline places 2,2-dibenzylcyclopentanone in line with the hindered 2,2-disubstituted-1,3-dicarbonyl class of substrates.[1] On the other hand, the expected enantiomer of the reduction product resulted when $BH_3$•THF or $BH_3$•$Me_2S$ were used as stoichiometric reductant (without *N*,*N*-diethylaniline) (Table 1, entries 1−2).

2,2-Bis-(4-bromobenzyl)cyclopentanone (**6**) was also studied in similar experiments with catalyst **3** and catecholborane, with and without *N*,*N*-diethylaniline in toluene at −50 °C, and displayed the same divergent behavior, as shown by the data in Table 2 for the reduction product **7**.

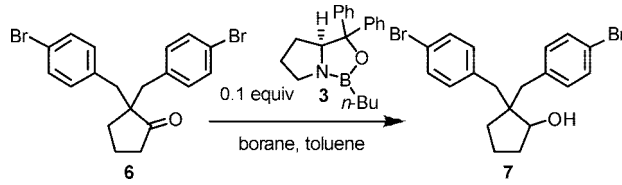
Since the effect of *N*,*N*-diethylaniline on oxazaborolidine catalyzed reduction of hindered ketones seemed to be specified for catecholborane, an interaction between diethylaniline and catecholborane was investigated by $^1$H and $^{11}$B NMR analysis. However, no evidence of such an interaction could be found. We further established that catecholborane is monomeric in benzene by cryoscopic determination of molecular weight, thus ruling out the complication of more than one form of the borane in hydrocarbon solution.

**Scheme 3**




We then investigated the possibility that a minor amount of impurity in the oxazaborolidine catalyst might be a factor. $^1$H NMR and $^{11}$B NMR analysis of a typical batch of catalyst, prepared using the standard method (heating (*S*)-1,1-diphenylpyrrolidinemethanol and *n*-butylboronic acid at prolonged reflux in toluene with a Dean−Stark apparatus containing heat-activated (250 °C) 4 Å molecular sieves for removal of water) revealed the presence of a few percent of the impurity **8**[3] (Scheme 2). In the past catalyst prepared in this way functioned well in most cases.

**Table 2.** Variation of Enantioselectivity in the Oxazaborolidine-Catalyzed Reduction of 2,2-(4-Bromobenzyl)-cyclopentanone with Coreactants

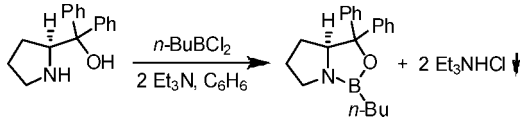



| entry[a] | borane (equiv) | $T$ (°C) | time | yield (%)[b] | ee (%)[c] | $[\alpha]_D$[d] |
|---|---|---|---|---|---|---|
| 1 | $BH_3$-$Me_2S$ (1.0) | 23 | 1 h | 99 | 95 | +2.9 |
| 2 | catecholborane (1.8) | −50 | 8 h | 97 | −94 | −2.9 |
| 3 | catecholborane (1.8)+$PhNEt_2$ (0.5) | −50 | 8 h | 98 | 93 | +2.8 |

[a] In each case the catalyst was prepared from (*S*)-1,1-diphenylpyrrolidinemethanol and *n*-$BuB(OH)_2$ by heating in toluene at reflux in a Dean−Stark apparatus containing 4 Å molecular sieves. [b] Isolated yield. [c] Determined by HPLC analysis using a Chiracel OD column. [d] Rotation determined in $CHCl_3$ solution ($c$ = 1.0).

It was possible to eliminate the impurity **8** by conducting the preparation of catalyst **3** in a Soxhlet apparatus containing a mixture of potassium hydride and sand for removal of water. When this very pure catalyst was used for the reduction of the Torgov diketone **1** with catecholborane in toluene at −50 °C the reduction product **2** was obtained in 89% yield and 93% ee, a result which is essentially the same as obtained earlier in the presence of *N*,*N*-diethylaniline. Thus, it is clear that the use of *N*,*N*-diethylaniline is unnecessary with catecholborane as reductant if pure catalyst **3** is used, and that its beneficial effect comes into play only when small amounts of the impurity **8** are present in the batch of catalyst **3** which is employed. Further, the deleterious effect of the impurity **8** is manifested only with hindered ketones which react more slowly and when catecholborane is used as the stoichiometric reductant.

**Scheme 4**




Studies using the hydrated oxazaborolidine **8** revealed a relatively slow reaction with catecholborane at −50 °C in toluene which is greatly accelerated upon addition of *N*,*N*-diethylaniline. The catalyzed reaction forms $H_2$ and the catecholboric anhydride **9**, as determined by NMR analysis (Scheme 3). These results imply that the beneficial effect of diethylaniline derives from its acceleration of the removal of the deleterious impurity **8** by conversion to the catalyst **3**. Reaction of the oxazaborolidine hydrate with *N*,*N*-diethylaniline and NaH in toluene cleanly converted it to the oxazaborolidine **3** as shown by by $^1H$ and $^{11}B$ NMR analysis. Catalyst **3** so prepared and catecholborane reduced diketone **1** to the hydroxy ketone **2** (in toluene at −50 °C) in high yield and 92% ee. In contrast, the reaction of the hydrate **8** and catecholborane alone with the Torgov diketone **1** gave principally the enantiomer of **2** (36% ee).

There are a number of possible reasons for the harmful effects of **8** in CBS reductions of hindered ketones and 1,3-diketones. Perhaps the most obvious possibility is that **8** can compete with the ketone substrate by binding to the complex of catecholborane and catalyst **3**, thus inhibiting the normal CBS reduction pathway. Another explanation is that the presence of **8** results in promotion of undesirable side reactions such as destruction of catecholborane or catalysis of ketonic reduction to form the enantiomer of the normal CBS reduction product.

Given the problems caused by the presence of impurity **8** in certain of the reductions catalyzed by **3** with catecholborane as reductant, we have investigated an alternative method[4] for the generation of catalyst **3** which avoids the possibility of forming **8**. Reaction of *n*-$BuBCl_2$ with (*S*)-1,1-diphenylpyrrolidinemethanol in benzene with 2 equiv of triethylamine rapidly formed **3** and a precipitate of $Et_3NHCl$. Simple filtration with exclusion of air and moisture provided a solution of pure **3** (Scheme 4). Use of **3** prepared in this way for the reduction of the Torgov diketone **1** with catecholborane gave the desired hydroxy ketone **2**, in 87% yield and 92% ee, and without the use of *N*,*N*-diethylaniline. *n*-$BuBCl_2$ was prepared from dichloroborane and 1-butene.[5]

(3) See, Jones, T. K.; Mohan, J. J.; Xavier, L. C.; Blacklock, T. J.; Mathre, D. J.; Sohar, P.; Jones, E. T. T.; Reamer, R. A.; Roberts, F. E.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 763–769.

(4) To a solution of (*S*)-1,1-diphenylpyrrolidinemethanol (253 mg, 1.0 mmol, from Aldrich) and triethylamine (280 mL, 2.0 mmol) in benzene (1 mL) in a 10-mL round-bottomed flask equipped with a stir bar was added *n*-$BuBCl_2$ (1 M in toluene, 1.0 mL, 1.0 mmol) at 23 °C. The resulting solution was heated to 40 °C for 1 h. After stirring at 23 °C for another 1 h, solvents were removed *in vacuo* (*ca*. 0.1 mmHg). The residue was diluted with benzene (2 mL) and the suspension was filtered through a sintered glass funnel under nitrogen. The ammonium salt was washed with benzene (5mL) and the benzene was removed *in vacuo* (*ca*. 0.1 mmHg). Toluene (5.0 mL) was added to provide a 0.20 M solution of the pure oxazaborolidine **3**.

This method of preparation of catalyst **3** may be advantageous for catalyzed reductions using catecholborane as reductant.

In conclusion, the beneficial effect of *N*,*N*-diethylaniline in the reduction of the Torgov diketone (**1**) mediated by catalyst **3** and catecholborane is due to the ability of this amine to catalyze the destruction of a minor impurity (**8**) in preparations of **3** by the process shown in Scheme 3.

(5) Soundararajan, R.; Matteson, D. S. *J. Org. Chem.* **1990**, *55*, 2274–2275.

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**Supporting Information Available:** Detailed experimental procedures and characterization for all new compounds and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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