

Acetophenone reduction with oxazaborolidine mediated ketone reduction. The model was developed using multivariate data analysis (MVA) to predict the ee's of reactions with a variety of chiral catalysts. The model responded well with the actual experimental results.

In a recent preliminary results of a study, showing that a simple quantitative structure-selectivity (QSSR) model based on catalyst structures can be used to predict the ee of the product. This model relates the ee of the product to a set of structure-based descriptors to observed differences in ee. The descriptors are based on constitutional, topological, and geometrical and physicochemical data.⁵ The results of literature case studies, involving a QSSR approach predicting the ee of ketone and enamide reductions with various chiral catalysts, were recently reported.¹ A similar approach has recently been used for the study of enzymatic resolution reactions.⁶

In this study, the QSSR model was used to predict the ee of the product. The model was developed using multivariate data analysis (MVA) to predict the ee's of reactions with a variety of chiral catalysts. The model responded well with the actual experimental results. The model was developed using multivariate data analysis (MVA) to predict the ee's of reactions with a variety of chiral catalysts. The model responded well with the actual experimental results.

2. Results and discussion

The oxazaborolidine mediated reduction of acetophenone was selected as the model reaction (Fig. 1). This type of reaction has been extensively studied^{7,8} and is applicable on an industrial scale.⁹⁻¹¹ The catalysts were

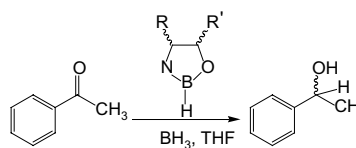


Figure 1. Acetophenone reduction with oxazaborolidines.

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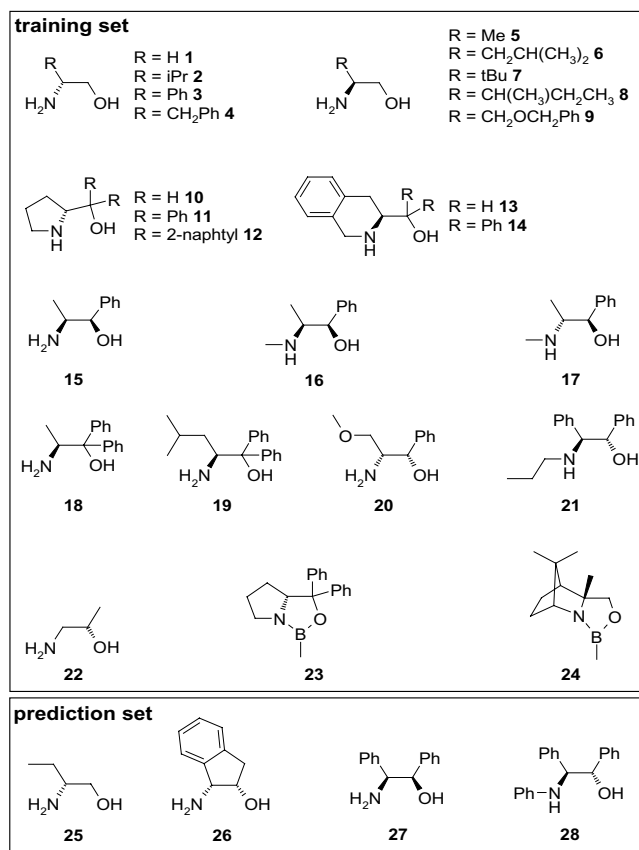


Figure 2. Aminoalcohol and oxazaborolidine structures.

synthesised in situ from an amino alcohol and borane. A selection of 26 commercially available aminoalcohols have been made, including natural amino acid derivatives and ephedrine. Two preformed oxazaborolidines are also included (Fig. 2).

The dataset required for modelling purposes needs to meet a number of criteria. First of all the data needs to be consistent, that is, all reactions have to be performed under similar conditions. Furthermore the data needs to be of good quality; preferably all reactions are performed in triplicate and the reproducibility needs to be high. For CBS reductions accurate and reproducible substrate addition feed rates are also important. These criteria are met by performing the reactions in a parallel fashion on an automated workstation.

The reactions in this study were performed on a Chemspeed ASW2000 workstation in 16 mL glass reactors. The reactions were done on 1 mmol scale at 25 °C in THF and BH₃·THF was used as the stoichiometric reducing agent. The acetophenone was slowly added over a 10 min period. The samples were analysed by chiral GC using an internal standard. All reductions went to completion, with the obtained ee's ranging from 0% to 98%. Some of the oxazaborolidines have been used in previous studies⁷ and the results obtained correspond with the previously reported results. Most of the reactions were performed more than once with the reproducibility proving to be excellent (Table 2).

For all oxazaborolidines, molecular descriptors were calculated from the oxazaborolidine 3D structures, which were obtained from molecular mechanics (MM⁺) calculations. Subsequently, the oxazaborolidines were split into a training set of 24 and a prediction set of 4 oxazaborolidines. For the training set, the descriptor data were fitted to the observed ee by partial least squares (PLS) regression.¹² The obtained QSSR model (Fig. 3) showed a good correlation ($R^2 = 0.978$) and satisfying predictive power ($Q^2 = 0.797$). The model was validated by predicting the product ee's in acetophenone reductions with oxazaborolidines based on aminoalcohols **25**, **26**, **27** and **28** (Table 1 and Fig. 3). It is noteworthy that whilst **25** and **26** might be expected to give large differences in selectivity, the discrimination between **27** and **28** is less clear-cut. Moreover, other combinations of training and prediction sets provided similarly satisfactory results.

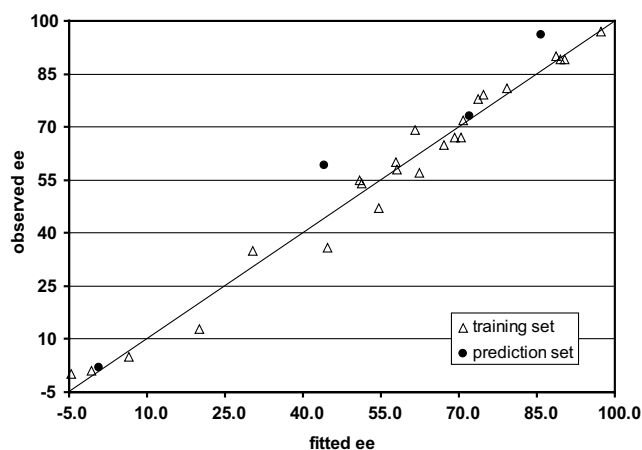


Figure 3. Observed versus fitted ee values.

Table 1. Results of the validation of the QSSR model

| Aminoalcohol | Fitted ee | Calculated ee |
|--------------|-----------|---------------|
| 25 | 73 | 72 |
| 26 | 96 | 86 |
| 27 | 59 | 44 |
| 28 | 2 | 1 |

In summary, a QSSR model has been developed, which is able to predict the enantioselectivity of oxazaborolidines in the reduction of acetophenone. The model uses catalyst-based molecular descriptors and does not require prior knowledge of the reaction mechanism or transition state. This approach only requires a short computational time. The model obtained can be used for in silico pre-screening of catalysts or chiral ligands to quickly identify promising candidates for further investigation. The current QSSR model is not yet able to predict the ee's exactly nor can it predict the configuration of the reaction product. However, it can clearly distinguish between oxazaborolidines that give high, moderate or low ee's. Further studies are ongoing to refine and extend the predictive power of the model and to apply this methodology to other chemistries.

Table 2. Results of the oxazaborolidine mediated reductions

| Entry | Compound # | Compound name | Mass balance (%) | Conversion (%) | Ee (%) ^a |
|-------|------------|---|------------------|----------------|---------------------|
| 1 | 1 | Aminoethanol | 91.6 | 100 | 1 |
| 2 | 1 | Aminoethanol | 91.2 | 100 | 0 |
| 3 | 2 | (<i>R</i>)-Valinol | 91.7 | 100 | 82 |
| 4 | 2 | (<i>R</i>)-Valinol | 96.0 | 100 | 80 |
| 5 | 2 | (<i>R</i>)-Valinol | 93.8 | 100 | 78 |
| 6 | 3 | (<i>R</i>)-2-Phenylglycinol | 91.1 | 100 | 90 |
| 7 | 3 | (<i>R</i>)-2-Phenylglycinol | 92.2 | 100 | 89 |
| 8 | 4 | (<i>R</i>)-2-Amino-3-phenyl-1-propanol | 89.7 | 100 | 72 |
| 9 | 4 | (<i>R</i>)-2-Amino-3-phenyl-1-propanol | 91.7 | 100 | 72 |
| 10 | 4 | (<i>R</i>)-2-Amino-3-phenyl-1-propanol | 89.2 | 99 | 71 |
| 11 | 4 | (<i>R</i>)-2-Amino-3-phenyl-1-propanol | 88.6 | 100 | 71 |
| 12 | 4 | (<i>R</i>)-2-Amino-3-phenyl-1-propanol | 90.3 | 100 | 70 |
| 13 | 5 | (<i>S</i>)-2-Amino-1-propanol | 94.7 | 100 | 56 |
| 14 | 5 | (<i>S</i>)-2-Amino-1-propanol | 92.5 | 100 | 56 |
| 15 | 5 | (<i>S</i>)-2-Amino-1-propanol | 96.4 | 100 | 54 |
| 16 | 6 | (<i>S</i>)-Leucinol | 94.0 | 100 | 69 |
| 17 | 6 | (<i>S</i>)-Leucinol | 93.9 | 100 | 68 |
| 18 | 6 | (<i>S</i>)-Leucinol | 95.8 | 99 | 67 |
| 19 | 6 | (<i>S</i>)-Leucinol | 96.0 | 100 | 66 |
| 20 | 7 | (<i>S</i>)- <i>tert</i> -Leucinol | 97.6 | 100 | 90 |
| 21 | 7 | (<i>S</i>)- <i>tert</i> -Leucinol | 97.4 | 100 | 89 |
| 22 | 8 | (<i>S</i>)-Isoleucinol | 96.6 | 100 | 80 |
| 23 | 8 | (<i>S</i>)-Isoleucinol | 96.2 | 100 | 79 |
| 24 | 9 | (<i>R</i>)-2-Amino-3-benzyloxy-1-propanol | 95.1 | 100 | 71 |
| 25 | 9 | (<i>R</i>)-2-Amino-3-benzyloxy-1-propanol | 95.5 | 100 | 67 |
| 26 | 9 | (<i>R</i>)-2-Amino-3-benzyloxy-1-propanol | 93.1 | 100 | 67 |
| 27 | 10 | (<i>R</i>)-(-)-2-(Hydroxymethyl)-pyrrolidinone (<i>R</i>)-prolinol | 91.5 | 100 | 62 |
| 28 | 10 | (<i>R</i>)-(-)-2-(Hydroxymethyl)-pyrrolidinone (<i>R</i>)-prolinol | 91.6 | 100 | 57 |
| 29 | 10 | (<i>R</i>)-(-)-2-(Hydroxymethyl)-pyrrolidinone (<i>R</i>)-prolinol | 90.6 | 100 | 56 |
| 30 | 11 | (<i>R</i>)- α,α -Diphenyl-2-pyrrolidinemethanol | 99.3 | 100 | 74 |
| 31 | 11 | (<i>R</i>)- α,α -Diphenyl-2-pyrrolidinemethanol | 93.7 | 100 | 72 |
| 32 | 12 | (<i>R</i>)- α,α -Dinaphthyl-2-pyrrolidinemethanol | 91.1 | 100 | 59 |
| 33 | 12 | (<i>R</i>)- α,α -Dinaphthyl-2-pyrrolidinemethanol | 95.7 | 100 | 56 |
| 34 | 13 | (<i>S</i>)-1,2,3,4-Tetrahydro-3-isoquinolinemethanol | 93.2 | 86 | 54 |
| 35 | 13 | (<i>S</i>)-1,2,3,4-Tetrahydro-3-isoquinolinemethanol | 91.5 | 76 | 53 |
| 36 | 14 | (<i>S</i>)-(-)-1,2,3,4-Tetrahydro- α,α -diphenyl-3- isoquinolinemethanol | 90.7 | 100 | 6 |
| 37 | 14 | (<i>S</i>)-(-)-1,2,3,4-Tetrahydro- α,α -diphenyl-3- isoquinolinemethanol | 90.6 | 100 | 3 |
| 38 | 15 | (1 <i>R</i> ,2 <i>S</i>)-(-)-Norephedrine | 92.7 | 100 | 86 |
| 39 | 15 | (1 <i>R</i> ,2 <i>S</i>)-(-)-Norephedrine | 96.8 | 100 | 84 |
| 40 | 15 | (1 <i>R</i> ,2 <i>S</i>)-(-)-Norephedrine | 98.2 | 100 | 83 |
| 41 | 16 | (1 <i>R</i> ,2 <i>S</i>)-(-)-Ephedrine | 95.5 | 100 | 33 |
| 42 | 16 | (1 <i>R</i> ,2 <i>S</i>)-(-)-Ephedrine | 95.1 | 100 | 33 |
| 43 | 16 | (1 <i>R</i> ,2 <i>S</i>)-(-)-Ephedrine | 92.3 | 100 | 30 |
| 44 | 17 | (1 <i>R</i> ,2 <i>R</i>)-(-)-Pseudoephedrine | 88.7 | 99 | 14 |
| 45 | 17 | (1 <i>R</i> ,2 <i>R</i>)-(-)-Pseudoephedrine | 89.8 | 100 | 13 |
| 46 | 18 | (<i>S</i>)-(-)-2-Amino-1,1-diphenyl-1-propanol | 90.9 | 100 | 52 |
| 47 | 18 | (<i>S</i>)-(-)-2-Amino-1,1-diphenyl-1-propanol | 97.0 | 100 | 49 |
| 48 | 18 | (<i>S</i>)-(-)-2-Amino-1,1-diphenyl-1-propanol | 93.3 | 100 | 47 |
| 49 | 18 | (<i>S</i>)-(-)-2-Amino-1,1-diphenyl-1-propanol | 92.0 | 100 | 42 |

(continued on next page)

Table 2. (continued)

| Entry | Compound # | Compound name | Mass balance (%) | Conversion (%) | Ee (%) ^a |
|-------|------------|--|------------------|----------------|---------------------|
| 50 | 19 | (S)-(-)-2-Amino-4-methyl-1,1-diphenyl-1-pentanol | 91.3 | 100 | 74 |
| 51 | 19 | (S)-(-)-2-Amino-4-methyl-1,1-diphenyl-1-pentanol | 94.5 | 100 | 64 |
| 52 | 19 | (S)-(-)-2-Amino-4-methyl-1,1-diphenyl-1-pentanol | 95.5 | 100 | 50 |
| 53 | 19 | (S)-(-)-2-Amino-4-methyl-1,1-diphenyl-1-pentanol | 95.4 | 100 | 49 |
| 54 | 20 | (1S,2S)-(+)-2-Amino-3-methoxy-1-phenyl-1-propanol | 96.0 | 100 | 67 |
| 55 | 20 | (1S,2S)-(+)-2-Amino-3-methoxy-1-phenyl-1-propanol | 91.8 | 100 | 63 |
| 56 | 21 | <i>erythro</i> -1,2-Diphenyl-2-(propylamino)-ethanol | 87.8 | 100 | 2 |
| 57 | 21 | <i>erythro</i> -1,2-Diphenyl-2-(propylamino)-ethanol | 91.6 | 92 | 1 |
| 58 | 22 | (S)-1-Amino-2-propanol | 90.3 | 100 | 36 |
| 59 | 22 | (S)-1-Amino-2-propanol | 90.1 | 100 | 36 |
| 60 | 22 | (S)-1-Amino-2-propanol | 89.3 | 100 | 36 |
| 61 | 23 | 1,4,10,10-Tetramethyl-3-oxa-5-aza-4-boratricyclo[5.2.1.0-2,6]-decane | 94.6 | 100 | 89 |
| 62 | 23 | 1,4,10,10-Tetramethyl-3-oxa-5-aza-4-boratricyclo[5.2.1.0-2,6]-decane | 94.8 | 100 | 89 |
| 63 | 24 | (R)-2-Methyl-CBS-oxazaborolidine | 92.6 | 100 | 98 |
| 64 | 24 | (R)-2-Methyl-CBS-oxazaborolidine | 93.6 | 100 | 96 |
| 65 | 25 | (R)-2-Amino-1-butanol | 90.6 | 98 | 74 |
| 66 | 25 | (R)-2-Amino-1-butanol | 89.7 | 100 | 74 |
| 67 | 25 | (R)-2-Amino-1-butanol | 91.8 | 100 | 73 |
| 68 | 25 | (R)-2-Amino-1-butanol | 91.6 | 100 | 72 |
| 69 | 25 | (R)-2-Amino-1-butanol | 99.9 | 99 | 71 |
| 70 | 25 | (R)-2-Amino-1-butanol | 94.6 | 100 | 71 |
| 71 | 26 | (1R,2S)-(+)- <i>cis</i> -1-Amino-2-indanol | 92.0 | 100 | 97 |
| 72 | 26 | (1R,2S)-(+)- <i>cis</i> -1-Amino-2-indanol | 93.8 | 100 | 97 |
| 73 | 26 | (1R,2S)-(+)- <i>cis</i> -1-Amino-2-indanol | 91.1 | 100 | 96 |
| 74 | 27 | (1R,2S)-2-Amino-1,2-diphenylethanol | 92.1 | 100 | 59 |
| 75 | 28 | <i>erythro</i> -2-Anilino-1,2-diphenyl-ethanol | 90.6 | 100 | 2 |
| 76 | 28 | <i>erythro</i> -2-Anilino-1,2-diphenyl-ethanol | 90.6 | 99 | 1 |
| 77 | Control | Blank/THF | 91.2 | 100 | 1 |
| 78 | Control | Blank/THF | 90.0 | 100 | 0 |
| 79 | Control | Blank/THF | 90.9 | 100 | 0 |

^a The 1% ee observed with the nonchiral aminoalcohol **1** and the control reactions indicate the error in the analytical method. The reproducibility was very good with the exception of compounds **18** and **19**, which is probably due to precipitation of the catalyst solution during the run.

3. Experimental

A stock solution (250 mL) of acetophenone (30.007 g, 0.250 mol) and 1,3,5-triisopropylbenzene (GC internal standard) (12.779 g, 0.0625 mol) in anhydrous THF was prepared. Stock solutions of 1.0 M of aminoalcohol (or oxazaborolidine) in anhydrous THF were prepared. These stock solutions were prepared in septum capped bottles in a glovebox under controlled moisture free inert atmosphere. CBS-oxazaborolidine **24** was used as a 1.0 M solution in toluene as purchased from Aldrich; *cis*-aminoindanol **26** was prepared in DCM. Borane-THF was used as purchased from Acros as a 1.0 M solution in THF. The reactions were executed in three sessions on the Chemspeed ASW2000 workstation. The 16 mL glass reactors were purged with argon-vacuum

cycles at 100 °C. Anhydrous THF, kept under argon, was used as the reservoir solvent. The acetophenone stock solution, the borane solution and the reactors were kept under argon during the execution of the run. After the prime and purge the Chemspeed was programmed to: set temperature to 25 °C, set vortex to 600 rpm, add 4000 µL of anhydrous THF, add 100 µL of aminoalcohol (or oxazaborolidine), add 1000 µL of borane solution, add 1000 µL of acetophenone solution over 10 min, stir for 3 h, take sample 50 µL and transfer to HPLC vial containing 1000 µL of MeOH.

The samples were analysed by chiral GC (Trace GC; Thermo Finnigan equipped with a CTC combipal autosampler) using a Chirasil-DEX CB 25 m × 0.25 mm column, with He at 5 mL/min as the mobile phase.

Molecular descriptors were calculated from the oxazaborolidines as 3D mol-files, minimised with an MM⁺ forcefield with HyperChem Pro 6.0 (Hypercube). The PLS model was prepared with the Simca-P version 10.0 (Umetrics) software package.

References and notes

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