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Oxazaborolidine mediated asymmetric ketone reduction: prediction of enantiomeric excess based on catalyst structure

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Abstract—The feasibility of enantiomeric excess (ee) prediction is demonstrated for asymmetric oxazaborolidine mediated ketone reduction. A quantitative structure-selectivity (QSSR) model of chiral oxazaborolidines was created by using multivariate data analysis. High-throughput methods and regression techniques were used to correlate the model with the ee's of reactions with a training set and to predict the ee's for an additional set of oxazaborolidines. The predicted ee's corresponded well with the actual values, indicating that the model is very useful for the initial selection of catalysts for screening experiments.

1. Introduction

In recent years, advances in high-throughput experimentation, experimental design and multivariate data analysis resulted in a significant increase in the screening and optimisation of (asymmetric) catalytic reactions.[1,2] However, the performance of a catalyst remains difficult to predict, especially for complex compounds such as pharmaceutical intermediates. Many factors, such as catalyst structures, solvents or additives, can have a huge impact on the yield and selectivity of a catalytic reaction. The efficiency of the screening process could be significantly enhanced if a catalyst could be pre-screened by using a computer model to identify the most promising candidates. This in silico screening allows the chemist to start with a focused list of promising catalysts and to quickly move to the optimisation of other important variables such as solvent, temperature and additive. Recently, progress has been made on predicting enantiomeric excess (ee) with different computational methods.[3] However, the calculation methods are relatively computationally intense. Furthermore, these methods require extensive knowledge of the transition state and the calculated transition state might not even be the one leading to the major product.[4]

Herein, we report 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 catalyst-based descriptors to observed differences in ee. The descriptors are based on constitutional, topological, 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]

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

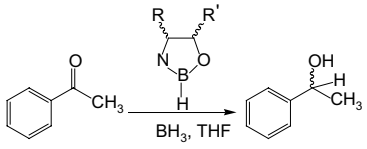

Figure 1. Acetophenone reduction with oxazaborolidines.

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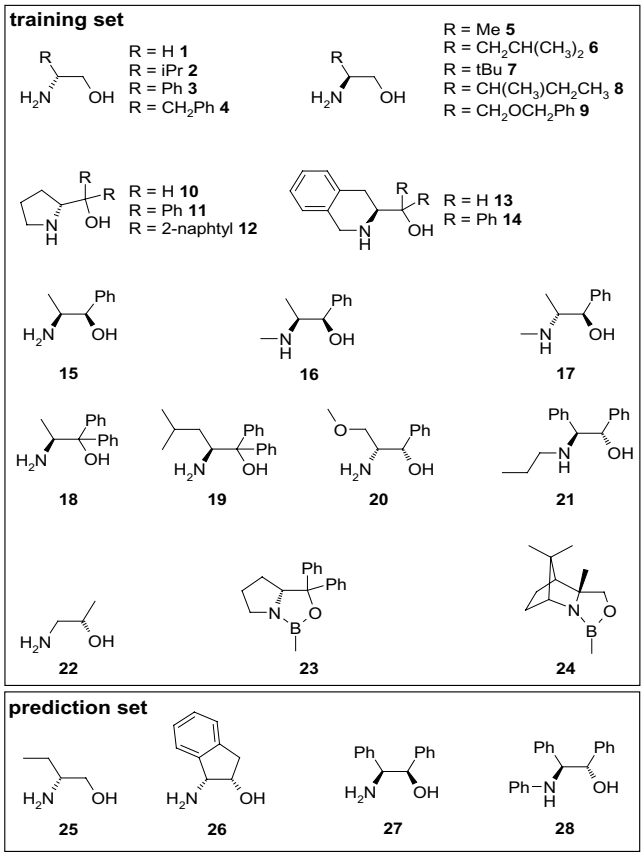

Figure 2. Aminoalcohol and oxazaborolidine structures.

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 ephedrines. 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 BH_3·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 studies[7] 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.

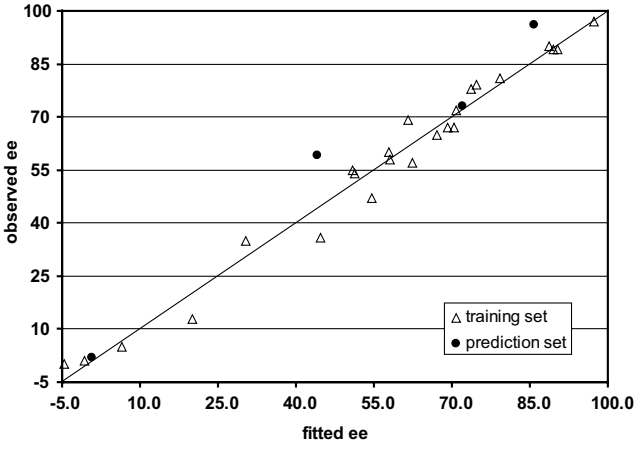

Figure 3. Observed versus fitted ee values.

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**	(*R*)-Valinol	91.7	100	82
4	**2**	(*R*)-Valinol	96.0	100	80
5	**2**	(*R*)-Valinol	93.8	100	78
6	**3**	(*R*)-2-Phenylglycinol	91.1	100	90
7	**3**	(*R*)-2-Phenylglycinol	92.2	100	89
8	**4**	(*R*)-2-Amino-3-phenyl-1-propanol	89.7	100	72
9	**4**	(*R*)-2-Amino-3-phenyl-1-propanol	91.7	100	72
10	**4**	(*R*)-2-Amino-3-phenyl-1-propanol	89.2	99	71
11	**4**	(*R*)-2-Amino-3-phenyl-1-propanol	88.6	100	71
12	**4**	(*R*)-2-Amino-3-phenyl-1-propanol	90.3	100	70
13	**5**	(*S*)-2-Amino-1-propanol	94.7	100	56
14	**5**	(*S*)-2-Amino-1-propanol	92.5	100	56
15	**5**	(*S*)-2-Amino-1-propanol	96.4	100	54
16	**6**	(*S*)-Leucinol	94.0	100	69
17	**6**	(*S*)-Leucinol	93.9	100	68
18	**6**	(*S*)-Leucinol	95.8	99	67
19	**6**	(*S*)-Leucinol	96.0	100	66
20	**7**	(*S*)-*tert*-Leucinol	97.6	100	90
21	**7**	(*S*)-*tert*-Leucinol	97.4	100	89
22	**8**	(*S*)-Isoleucinol	96.6	100	80
23	**8**	(*S*)-Isoleucinol	96.2	100	79
24	**9**	(*R*)-2-Amino-3-benzyloxy-1-propanol	95.1	100	71
25	**9**	(*R*)-2-Amino-3-benzyloxy-1-propanol	95.5	100	67
26	**9**	(*R*)-2-Amino-3-benzyloxy-1-propanol	93.1	100	67
27	**10**	(*R*)-(−)-2-(Hydroxymethyl)-pyrrolidinone ((*R*)-prolinol)	91.5	100	62
28	**10**	(*R*)-(−)-2-(Hydroxymethyl)-pyrrolidinone ((*R*)-prolinol)	91.6	100	57
29	**10**	(*R*)-(−)-2-(Hydroxymethyl)-pyrrolidinone ((*R*)-prolinol)	90.6	100	56
30	**11**	(*R*)-α,α-Diphenyl-2-pyrrolidinemethanol	99.3	100	74
31	**11**	(*R*)-α,α-Diphenyl-2-pyrrolidinemethanol	93.7	100	72
32	**12**	(*R*)-α,α-Dinaphthyl-2-pyrrolidinemethanol	91.1	100	59
33	**12**	(*R*)-α,α-Dinaphthyl-2-pyrrolidinemethanol	95.7	100	56
34	**13**	(*S*)-1,2,3,4-Tetrahydro-3-isoquinolinemethanol	93.2	86	54
35	**13**	(*S*)-1,2,3,4-Tetrahydro-3-isoquinolinemethanol	91.5	76	53
36	**14**	(*S*)-(−)-1,2,3,4-Tetrahydro-α,α-diphenyl-3-isoquinolinemethanol	90.7	100	6
37	**14**	(*S*)-(−)-1,2,3,4-Tetrahydro-α,α-diphenyl-3-isoquinolinemethanol	90.6	100	3
38	**15**	(1*R*,2*S*)-(−)Norephedrine	92.7	100	86
39	**15**	(1*R*,2*S*)-(−)Norephedrine	96.8	100	84
40	**15**	(1*R*,2*S*)-(−)Norephedrine	98.2	100	83
41	**16**	(1*R*,2*S*)-(−)-Ephedrine	95.5	100	33
42	**16**	(1*R*,2*S*)-(−)-Ephedrine	95.1	100	33
43	**16**	(1*R*,2*S*)-(−)-Ephedrine	92.3	100	30
44	**17**	(1*R*,2*R*)-(−)-Pseudoephedrine	88.7	99	14
45	**17**	(1*R*,2*R*)-(−)-Pseudoephedrine	89.8	100	13
46	**18**	(*S*)-(−)-2-Amino-1,1-diphenyl-1-propanol	90.9	100	52
47	**18**	(*S*)-(−)-2-Amino-1,1-diphenyl-1-propanol	97.0	100	49
48	**18**	(*S*)-(−)-2-Amino-1,1-diphenyl-1-propanol	93.3	100	47
49	**18**	(*S*)-(−)-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**	(1*S*,2*S*)-(+)-2-Amino-3-methoxy-1-phenyl-1-propanol	96.0	100	67
55	**20**	(1*S*,2*S*)-(+)-2-Amino-3-methoxy-1-phenyl-1-propanol	91.8	100	63
56	**21**	*erythro*-1,2-Diphenyl-2-(propylamino)-ethanol	87.8	100	2
57	**21**	*erythro*-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-bor-atricyclo[5.2.1.0-2,6]-decane	94.6	100	89
62	**23**	1,4,10,10-Tetramethyl-3-oxa-5-aza-4-bor-atricyclo[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**	(1*R*,2*S*)-(+)-*cis*-1-Amino-2-indanol	92.0	100	97
72	**26**	(1*R*,2*S*)-(+)-*cis*-1-Amino-2-indanol	93.8	100	97
73	**26**	(1*R*,2*S*)-(+)-*cis*-1-Amino-2-indanol	91.1	100	96
74	**27**	(1*R*,2*S*)-2-Amino-1,2-diphenylethanol	92.1	100	59
75	**28**	*erythro*-2-Anilino-1,2-diphenyl-ethanol	90.6	100	2
76	**28**	*erythro*-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.

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