A New Family of Modular Chiral Ligands for the Catalytic Enantioselective Reduction of Prochiral Ketones

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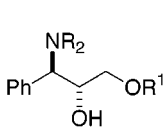
A family of enantiomerically pure (4*R*,5*R*)-2-alkyl-4-phenyl-5-(*R*-oxymethyl)-1,3,2-oxazaborolidines (**5**) [boron substituent: H, CH_3, *n*-C_4H_9; R-oxy group: CH_3O, $CH_3OCH_2CH_2O$, $CH_3(OCH_2CH_2)_2O$, $PhCH_2O$, Ph_2CHO, Ph_3CO] has been prepared from (2*S*,3*S*)-2,3-epoxy-3-phenylpropanol (**2**) through a four-step sequence involving protection of the alcohol, regioselective ring-opening of the epoxide with sodium azide in acetonitrile in the presence of $LiClO_4$, reduction of the azido group (H_2/Pd−C/MeOH or $NaBH_4$/THF−MeOH), and formation of the oxazaborolidine ring with the appropriate boron reagent. Both the boron substituent and the R-oxy group have been optimized for maximal enantioselectivity in the reduction of prochiral ketones with borane. The optimal oxazaborolidine (**5a-Me**) [boron substituent: CH_3; R-oxy group: CH_3O] has been employed (10% molar amount, THF, 0 °C to room temperature) in the reduction of a representative family of 10 substrates comprising alkyl aryl ketones and dialkyl ketones. In these reductions, **5a-Me** induces the formation of secondary alcohols of *S* configuration with high enantioselectivity (93% mean enantiomeric excess). The origin of the enantioselectivity in the reduction has been rationalized by means of semiempirical AM1 calculations.

Introduction

Modularly constructed ligands, which allow the fast optimization of catalytic properties for a given application, are increasingly recognized as a major advancement at both the academic and the industrial levels. We have recently applied this philosophy to the preparation of a family of enantiopure amino alcohol ligands **1** starting from readily available enantiopure epoxy alcohol **2**. Through an iterative process, the structural parameters key to high catalytic efficiency in the addition of diethylzinc to aldehydes were established. These parameters turned out to be the steric bulk of the R-oxy group and the nature of the dialkylamino substituent as a nitrogen-containing six-membered ring.[1] Further optimization of the dialkylamino substituent through a mechanism-guided molecular design[2] led to **3a**, a most convenient ligand for the ethylation of aldehydes.

The structural specification of the optimal modules shows some transferability among related families of amino alcohols acting in the same reaction. Thus, the systematic study of perhydroazines as dialkylamino components in a family of amino alcohols derived from synthetic, yet enantiomerically pure, triphenylethylene oxide has led to the development of a superior enantioselective catalyst, **3b**, for the addition of diethylzinc to α-substituted aldehydes.[3]



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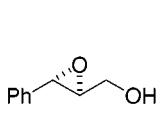

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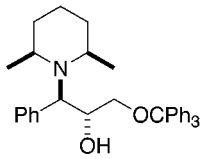

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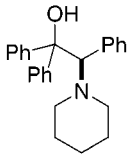

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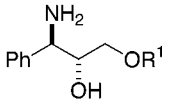

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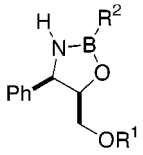

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The catalytic enantioselective reduction of prochiral ketones stands as an alternative and complementary method for the synthesis of chiral secondary alcohols. In particular, the oxazaborolidine-mediated enantioselective reduction of ketones with borane[4] is a well-established methodology: It has been applied with success to substrates of many different types, and the efficient catalytic cycle involved in the process has even been compared to the action mode of enzymes.[4b]

From a mechanistic point of view, the amino alcohol-mediated alkylation of aldehydes[5] and the oxazaborolidine-mediated reduction of ketones[6] bear many common characteristics (Figure 1): In both reactions, a heterocyclic five-membered ring formed from an amino alcohol and the corresponding reagent act as a disymmetric

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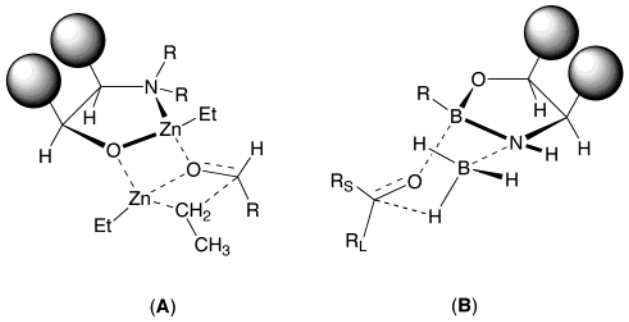


Figure 1. Schematic representation of the transition states in the amino alcohol-mediated reductive alkylation of aldehydes and the oxazaborolidine-mediated reduction of ketones.

template onto which the reacting molecules coordinate. These templates present a central heteroatom with Lewis acid character (zinc or boron) flanked in each case by two atoms with Lewis base character. It is assumed that in both reactions coordination of the carbonyl compound takes place at the Lewis acidic site, and the main difference between the reacting complexes lies on the Lewis base type atom where the reagent coordinates: Diethylzinc at oxygen[5] and borane at nitrogen.[6]

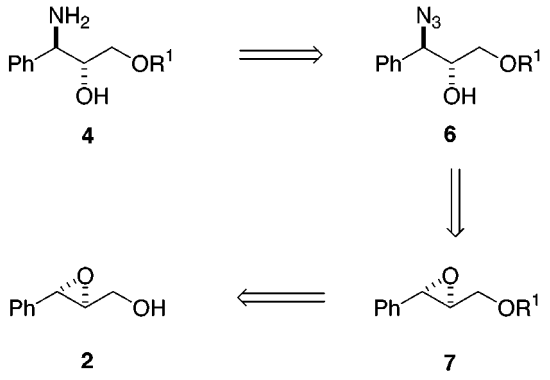
In view of these similarities, it is not surprising that structurally related amino alcohols have been employed as ligands with similar results for both types of chemistry.[7] According to these precedents, we considered that the free amino alcohols **4** could be convenient precursors to catalytically active oxazaborolidines. They belong to a structural type that has not previously been tested in the enantioselective reduction of ketones and contain in their structures the additional feature of the R^1-oxymethyl substituent that allows gradual modification of catalytic behavior in order to improve enantioselectivity.

The work described here details our efforts in the preparation of an optimized oxazaborolidine catalyst **5** for the enantioselective reduction of ketones, derived from amino alcohols **4**, through a modular optimization process involving both the alkoxy group OR^1 and the substituent at boron.

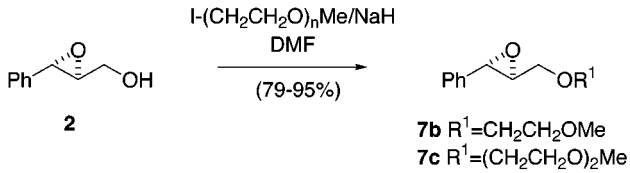
Results and Discussion

Synthesis of Amino Alcohols 4. The synthetic strategy envisaged for the conversion of epoxy alcohol **2** into amino alcohols **4**, precursors to oxazaborolidines **5**, is presented in retrosynthetic fashion in Scheme 1. In this strategy, the amino group comes from the reduction of an azide that, in turn, is introduced on epoxy ethers **7** by means of a well-precedented[8] regioselective ring opening. An initial protection of **2** would be the ultimate source of these epoxy ethers. This protection step is an

Scheme 1



Scheme 2



important source of diversity with high relevance for the purposes of this research, since groups R^1 with greatly different steric and electronic characteristics can be in principle introduced in the molecule without interference with the epoxide.

For the first part of the sequence, epoxy alcohol **2** was subjected to a variety of protection schemes. The preparation of compounds **7a** and **7d**−**f** (which are also key intermediates in the synthesis of ligands **1**) has already been reported.[1] In these alkylations, which require the intermediate formation of a metal alkoxide (NaH/DMF), low-temperature (−20 to 0 °C) conditions were used to prevent competing reactions. Under these conditions, the alkylations took place devoid of any detectable side reaction.

Along with these derivatives, designed to test the effect of the steric bulk of R^1 on the catalytic properties of the target oxazaborolidines, compounds **7b**,**c**, containing ethyleneglycol derived R^1 groups, were also prepared to provide models of oxazaborolidines anchored to poly(ethylene glycol) resins with expected increased binding ability of the ligand in the catalytic process. In these cases (Scheme 2), an excess of base and alkylating agent was required to obtain the final epoxy ethers in good yield, as elimination on the alkyl halide is a competing reaction even at 0 °C. A 79% yield was recorded for **7b** with a 6-fold excess of NaH and alkyl iodide. If the amount of both the base and alkylating agent is further increased (10-fold excess), the alkylation reaction takes then place very selectively (95% yield for **7c**).

As for the regioselective and stereospecific ring-opening step of epoxy ethers **7** with an azide-delivering reagent, Crotti's method[8d] (which involves the use of sodium azide in a 5 M $LiClO_4$ solution in acetonitrile) was used. Under these conditions, the intermediate azido alcohols **6a**−**f** were obtained in quantitative yield and were further converted into the final amino alcohols without purification. It is worth mentioning that the ring-opening step proceeds with complete regio- and stereospecificity, since NMR data are only in agreement with the diastereomerically pure anti azido alcohol exclusively arising from nucleophilic attack at C-3 of the epoxy ether. Two different procedures were used to reduce the azido to the

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Scheme 3

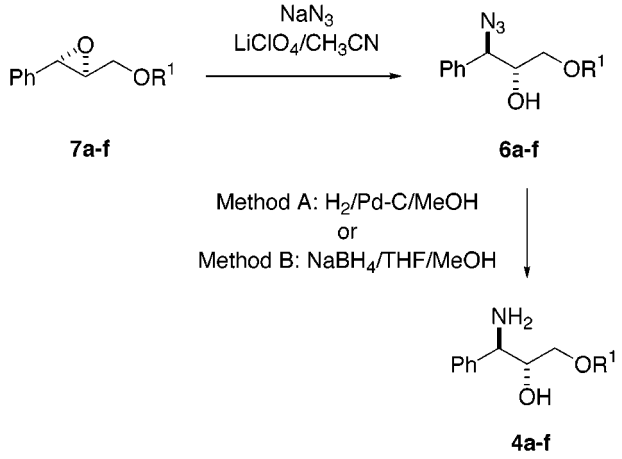

Table 1. Lithium Perchlorate-Induced Regioselective Ring Opening of Epoxy Ethers 7a−f by Sodium Azide Followed by Reduction of the Azido Group[a]

R^1	epoxy ether	reduction condns	product	overall yield (%)
Me	**7a**	method A, 36 h, rt	**4a**	91
CH_2CH_2OMe	**7b**	method A, 15 h, rt	**4b**	84
$(CH_2CH_2O)_2Me$	**7c**	method A, 36 h, rt	**4c**	81
CH_2Ph	**7d**	method B, 17 h, 55−60 °C	**4d**	92
$CHPh_2$	**7e**	method B, 8 h, 55−60 °C	**4e**	73
CPh_3	**7f**	method B, 23 h, 55−60 °C	**4f**	87

[a] All the ring-opening reactions were performed treating the starting epoxy ether **7a**−**f** with a 5-fold excess of sodium azide in a 5 M solution of $LiClO_4$ in acetonitrile at 55 °C for 24 h.

amino group depending on the stability of the protecting group R^1 toward reducing agents (Scheme 3). In those cases where R^1 is stable under hydrogenolytic conditions (**6a**−**c**), H_2 with Pd/C in MeOH was chosen as the reducing agent. Amino alcohols **4a**−**c** were obtained in this way in high overall yields (81−91%; see Table 1). Hydrogenolysis-sensitive azido alcohols (**6d**−**f**) were reduced with sodium borohydride in THF/MeOH[9] as these conditions turned out to be harmless to benzylic ethers. Overall yields for the preparation of **4d**−**f** were high as well, ranging from 73 to 92% (Table 1).

From a practical perspective, it is important to point out that the preparation of amino alcohols **4** has been easily carried out at the multigram scale without yield decrease. Even in this case, purification of the rather polar final products can be easily done by a short pad column chromatography following the reduction step, since both azido reduction conditions are very clean and efficient.

Ligand Optimization through the Catalytic Enantioselective Reduction of Prochiral Ketones. The oxazaborolidine-mediated catalytic enantioselective reduction of ketones by borane, introduced by Corey[6,10] following the pioneering work by Itsuno,[11] represents a paradigmatical example of "ligand-accelerated process":[12] Over the past years, continuing interest on this process has led to the development of new efficient borane reducing agents[13] and catalysts based on the oxazaborolidine structure.[13a,14] Once the family of amino alcohols **4** had been successfully prepared, we undertook studies directed to their conversion into oxazaborolidines **5**, with the purpose of studying them as chiral catalysts in this reaction. The functionalized amino alcohols **4** offer the possibility of systematic variations of steric, electronic, and binding characteristics of the ligand in order to achieve an improved catalytic behavior, while the substituent at boron represents an additional source of diversity.

Boron unsubstituted oxazaborolidines **5-H**, analogous to the ones initially used by Corey, were generated in situ from **4** by treatment of the amino alcohol with BH_3·Me_2S (BMS)[14h] as shown in Scheme 4. *B*-Alkylated oxazaborolidines, less air and moisture sensitive than the *B*-H analogues,[10a, 13a] have been described as more robust catalysts that can be used with no loss in the stereocontrol of the reaction. In the present instance, *B*-methyl oxazaborolidines (**5-Me**) have been easily prepared in toluene solution from amino alcohols **4** and methylboroxine,[14c] and *B*-butyl oxazaborolidine **5-Bu** from the amino alcohol and butylboronic acid,[13a] also in toluene (see Scheme 4). The solutions of **5-Me** and **5-Bu** could be stored at room temperature under nitrogen atmosphere for extended periods of time without appreciable decomposition or decrease in activity.

As the initial point in our reactivity study, we used the unsubstituted oxazaborolidines **5-H** derived from **4a**−**f** as the chiral catalysts, and we tested the optimal protecting group R^1 to achieve optimal catalytic properties in the enantioselective reduction of 1-phenylethan-1-one (**8a**) and 2-chloro-1-phenylethan-1-one (**8b**) (Scheme 5). All reactions were run at room temperature in THF

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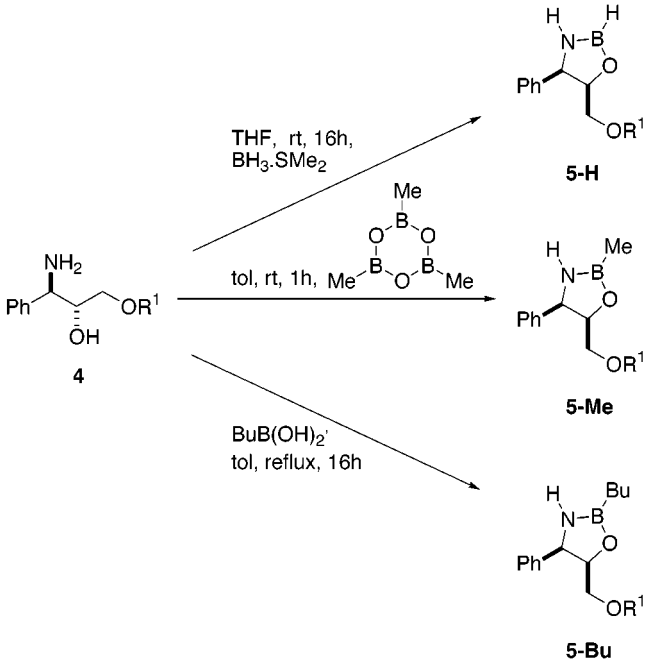
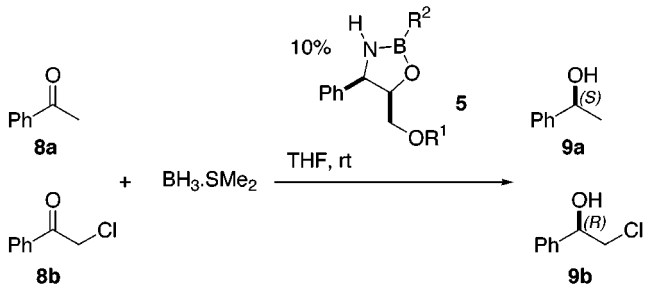
Scheme 4



Scheme 5



using BMS as the reducing agent and a 10% molar amount (with respect to the ketone) of oxazaborolidine catalyst. The starting ketone was slowly added (1 h) onto the corresponding catalyst solution with the aid of a syringe pump. Once the addition had been completed, conversion was very high so that the reactions could be quenched without delay (a 10 min stirring period was normally introduced).

The results obtained in the reduction of **8a** mediated by oxazaborolidines **5-H** derived from **4a**−**f** are shown in Table 2 (entries 1−6). An important conclusion can be drawn from these results. The best enantioselectivity was recorded for the less bulky protecting group (94% ee for R^1 = Me, entry 1). Much lower stereoselectivities were observed with R^1 = trityl (72% ee, entry 6). For the rest of ligands, ee's ranged between 81% and 91% as expected for protecting groups with a size comprised between a methyl and a trityl group. In this respect, it is interesting to note the existence of a regularity in the decrease of enantioselectivity upon increasing the number of phenyl groups and, hence, the bulkiness, in the protecting group (91% ee for R^1 = benzyl, 81% ee for R^1 = benzyhydryl and 72% ee for R^1 = trityl).

The same tendency was observed for **8b** under the same reaction conditions and with the same chiral catalyst (entries 13−18 in Table 2). The lowest stereoinduction was recorded for the largest protecting group (84% ee for R^1 = Tr). For any other specification of R^1, selectivities were higher and ranged from 88 to 91%. With this ketone, oxazaborolidines **5a**−**c** [R^1 = Me, R^1= CH_2CH_2OMe and R^1=$(CH_2CH_2O)_2Me$, respectively] induced the highest stereoselectivity in the reduction (91% ee in all three cases).

To study the possibility of cross-dependence between the R^1 and the boron substituents with respect to enantioselectivity, chiral catalysts **5-Me** derived from **4a**−**f** were also evaluated in the reduction of prochiral compounds **8a** and **8b**. Results are shown in Table 2 (entries 7−12 for 1-phenylethan-1-one **8a** and entries 19−24 for 2-chloro-1-phenylethan-1-one **8b**). In full agreement with the results observed for unsubstituted oxazaborolidines, steric congestion around the $-CH_2O-$ unit is detrimental to stereoselectivity in the reduction of prochiral ketones. Again, the most efficient catalyst is the one incorporating the less bulky substituent as the protecting group (**5a-Me**, R^1 = Me). Oxazaborolidine **5a-Me** induced the reduction of ketone **8a** with a 96% ee (entry 7) and in the case of **8b**, with a 94% ee (entry 19). On the contrary, catalyst **5f-Me**, which incorporates the bulkiest R^1 group in the series, induced the lowest stereoselectivity in the reduction of **8a** (85% ee, entry 12) and **8b** (82% ee, entry 24). These results tend to indicate that oxazaborolidines **5** behave as truly modular and that the variable structural elements (R^1 and the boron substituent) can be optimized separately.

When the whole series of results with *B*-H and *B*-Me oxazaborolidines are compared (entries 1−6 and 13−18 for *B*-H and 7−12 and 19−24 for *B*-Me), it becomes clear that the *B*-Me derivatives are better catalysts. To complete the optimization of this second parameter in catalysts **5**, the *B*-Bu substituted oxazaborolidine derived from the amino alcohol containing an optimal R^1 group (**4a**) was studied in the reduction of **8a** and **8b** (see entries 25 and 26 in Table 2). As it can be seen, the results obtained with this *B*-Bu-substituted oxazaborolidine did not represent any improvement over the corresponding ones with the *B*-Me catalyst, so that this possibility was not further investigated.

For the best catalyst in the series (**5a-Me**), we have investigated the effect of temperature on the turnover and stereoselectivity of the reaction (see Scheme 6 and Table 3). As the temperature was lowered from room temperature to 0 °C, the turnover of the system was significantly decreased. Even after extended reaction times (2 h addition plus 75 min additional stirring), conversions were 78% for **8a** and 71% for **8b**. As for the stereoselectivity, the ee of the reduction products decreased from 96 to 65% in the case of **8a** and from 94 to 68% in the case of **8b**. On the other hand, carrying out the reaction at 45 °C, led to the final product with practically no loss in the enantioselectivity for both studied ketones. According to this observation, the optimal temperature for the use of **5a-Me** as a catalyst seems to be 22 °C. Interestingly, working at temperatures slightly above this value seems to exert no negative influence on the enantioselectivity of the process, so that strict control of the temperature is not necessary. In any case, as it will be discussed later, adjustment of the optimal reaction temperature may require further refinement in some instances.

Enantioselective Reduction of a Representative Set of Ketones Catalyzed by the Optimized Oxazaborolidine 5a-Me. As a confirmation of the validity of the optimization process performed on catalysts **5**, the optimized oxazaborolidine **5a-Me** was used in the reduc-

Table 2. Effect of the R^1 an R^2 Groups in the Catalytic Enantioselective Reduction of Prochiral Ketones[a] 8a,b Leading to Alcohols 9a,b[b] Mediated by Chiral Oxazaborolidines 5

entry	chiral catalyst	R^1	R^2	starting ketone	resulting alcohol	conversion[c] (%)	selectivity[d] (%)	ee[e] (%)
1	**5a-H**	Me	H	**8a**	(*S*)-**9a**	>99	>99	**94**
2	**5b-H**	CH_2CH_2OMe	H	**8a**	(*S*)-**9a**	>99	>99	**86**
3	**5c-H**	$(CH_2CH_2O)_2Me$	H	**8a**	(*S*)-**9a**	88	>99	**81**
4	**5d-H**	CH_2Ph	H	**8a**	(*S*)-**9a**	>99	98	**91**
5	**5e-H**	$CHPh_2$	H	**8a**	(*S*)-**9a**	87	99	**81**
6	**5f-H**	CPh_3	H	**8a**	(*S*)-**9a**	83	99	**72**
7	**5a-Me**	Me	Me	**8a**	(*S*)-**9a**	>99	>99	**96**
8	**5b-Me**	CH_2CH_2OMe	Me	**8a**	(*S*)-**9a**	>99	>99	**94**
9	**5c-Me**	$(CH_2CH_2O)_2Me$	Me	**8a**	(*S*)-**9a**	>99	>99	**95**
10	**5d-Me**	CH_2Ph	Me	**8a**	(*S*)-**9a**	>99	>99	**92**
11	**5e-Me**	$CHPh_2$	Me	**8a**	(*S*)-**9a**	>99	>99	**95**
12	**5f-Me**	CPh_3	Me	**8a**	(*S*)-**9a**	86	>99	**85**
13	**5a-H**	Me	H	**8b**	(*R*)-**9b**	>99	>99	**91**
14	**5b-H**	CH_2CH_2OMe	H	**8b**	(*R*)-**9b**	>99	92	**91**
15	**5c-H**	$(CH_2CH_2O)_2Me$	H	**8b**	(*R*)-**9b**	>99	94	**91**
16	**5d-H**	CH_2Ph	H	**8b**	(*R*)-**9b**	>99	98	**88**
17	**5e-H**	$CHPh_2$	H	**8b**	(*R*)-**9b**	>99	>99	**89**
18	**5f-H**	CPh_3	H	**8b**	(*R*)-**9b**	>99	>99	**84**
19	**5a-Me**	Me	Me	**8b**	(*R*)-**9b**	>99	>99	**94**
20	**5b-Me**	CH_2CH_2OMe	Me	**8b**	(*R*)-**9b**	>99	90	**92**
21	**5c-Me**	$(CH_2CH_2O)_2Me$	Me	**8b**	(*R*)-**9b**	>99	>99	**89**
22	**5d-Me**	CH_2Ph	Me	**8b**	(*R*)-**9b**	>99	>99	**92**
23	**5e-Me**	$CHPh_2$	Me	**8b**	(*R*)-**9b**	>99	>99	**92**
24	**5f-Me**	CPh_3	Me	**8b**	(*R*)-**9b**	>99	>99	**82**
25	**5a-Bu**	Me	Bu	**8a**	(*S*)-**9a**	>99	>99	**95**
26	**5a-Bu**	Me	Bu	**8b**	(*R*)-**9b**	96	>99	**85**

[a] All reactions were performed in THF under N_2 at room temperature, using a $BH_3{\cdot}SMe_2$/ketone/catalyst molar ratio of 1.2/1/0.1. A solution of the ketone in THF was added onto a solution of the catalyst over a period of 1 h with the aid of a syringe pump. Acidic quenching was made 10 min after. [b] The absolute configuration of the final alcohols has been established by comparing the sign of the optical rotation with reported values for (*S*)-1-phenylethanol and (*R*)-2-chloro-1-phenylethanol. [c] Determined by integration of residual starting material in front of all new products in the gas chromatogram of the reaction crude. [d] Determined by integration of the reduction products (both enantiomers) in front of other reaction products. [e] By GC using a β-DEX 120 column.

Scheme 6

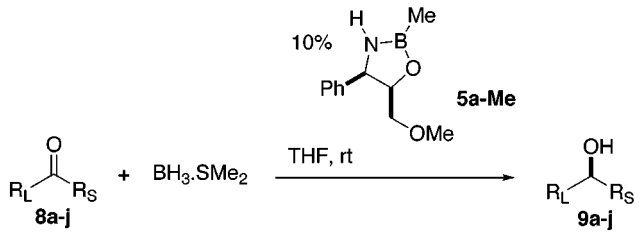


Table 3. Influence of the Temperature on the Catalytic Enantioselective Reduction of Ketones[a] 8a,b Leading to Alcohols 9a,b[b] Mediated by Chiral Oxazoborolidine 5a-Me

entry	chiral catalyst	*T* (°C)	starting ketone	resulting alcohol	conversion[c] (%)	selectivity[d] (%)	ee[e] (%)
1	**5a-Me**	0	**8a**	(*S*)-**9a**	78	>99	**65**
2	**5a-Me**	rt	**8a**	(*S*)-**9a**	>99	>99	**96**
3	**5a-Me**	45	**8a**	(*S*)-**9a**	>99	>99	**95**
4	**5a-Me**	0	**8b**	(*R*)-**9b**	71	>99	**68**
5	**5a-Me**	rt	**8b**	(*R*)-**9b**	>99	>99	**94**
6	**5a-Me**	45	**8b**	(*R*)-**9b**	>99	>99	**93**

[a–e] As described in Table 2 except for the reaction time in experiments at 0 °C (2 h addition plus 75 min stirring before quenching).

tion of a family of structurally diverse ketones including several alkyl aryl and dialkyl ketones (Scheme 6). Results on catalyst efficiency (conversion and selectivity) and enantiomeric excess of the final secondary alcohols have been collected in Table 4. Working at room temperature and using a 10% molar amount of oxazaborolidine catalyst, conversions were complete after short reaction

Table 4. Catalytic Enantioselective Reduction of a Family of Prochiral Ketones[a] 8a–j Leading to Alcohols 9a–j[b] Mediated by Chiral Oxazaborolidine 5a-Me

starting ketone	resulting alcohol	conversion[c] (%)	selectivity[d] (%)	ee[e] (%)
1-phenylethan-1-one (**8a**)	(*S*)-**9a**	>99	>99	**96**
2-chloro-1-phenylethan-1-one (**8b**)	(*R*)-**9b**	>99	>99	**94**
1-(3-methoxyphenyl)ethan-1-one (**8c**)	(*S*)-**9c**	>99	>99	**97**
1-(3-chlorophenyl)ethan-1-one (**8d**)	(*S*)-**9d**	>99	>99	**94**
1-(4-chlorophenyl)ethan-1-one (**8e**)	(*S*)-**9e**	>99	>99	**93**
3,3-dimethylbutan-2-one (**8f**)	(*S*)-**9f**	>99	>99	**97**
1-phenylpropan-1-one (**8g**)	(*S*)-**9g**	94	>99	**90**[f]
1,2,3,4-tetrahydronaphthalen-1-one (**8h**)	(*S*)-**9h**	>99	>99	**98**[g]
1-(2-methoxyphenyl)ethan-1-one (**8i**)	(*S*)-**9i**	>99	98	**92**[h]
1-cyclohexylethan-1-one (**8j**)	(*S*)-**9j**	>99	>99	**79**[i]

[a–d] As described in Table 2. [e] By GC using a β-DEX 120 column for **8a**–**i** and a α-DEX 120 column for **8j**. [f] The reaction was performed at 0 °C. Enantioselectivity at other temperatures, ee (%)/°C: 78/-10; 87/10; 85/22; 82/33. [g] The reaction was performed at 0 °C. Enantioselectivity at other temperatures, ee (%)/°C: 97/5; 87/22. [h] The reaction was performed at 10 °C. Enantioselectivity at other temperatures, ee (%)/°C: 85/0; 86/22; 83/33. [i] Enantioselectivity at other temperatures, ee (%)/°C: 59/0; 79/10; 77/33.

times (1 h addition plus 10 min stirring), and the reductions took place in a very clean manner (selectivity >99%). With respect to enantioselectivity, alcohols **9a**–**f**

were obtained with >93% ee, while enantiomeric purity was slightly lower in the other cases (**9g**−**j**). By progressive lowering of the reaction temperature, a point with maximal enantioselectivity could be located in the reduction of **8g**−**i**. Maximal enantioselectivities for these reductions are provided in the corresponding entries in Table 4, while enantioselectivities at other studied temperatures are given as footnotes. Up to 11 points in ee (from 87 to 98%) can be gained in the reduction of 1,2,3,4-tetrahydronaphthalen-1-one (**8h**) by simply lowering the reaction temperature from 22 to 0 °C. No increase of enantiomeric purity of the resulting alcohol (79% ee) could be recorded through variation of the reaction temperature in the case of 1-cyclohexylethan-1-one (**8j**). Much in the same way, the use of higher amounts of **5a-Me** in the reduction (up to a stoichiometric amount) did not provoke any improvement in the enantioselectivity of the reaction. In this context, it is worth noting that the same reduction, when performed with the CBS reagent,[10a] affords alcohol **9j** of unusually low enantiomeric purity (84% ee).

When the overall performance of **5a-Me** is considered, the mean enantiomeric excess of alcohols **9a**−**j** obtained with a 10% molar amount of the chiral agent is found to be 93%. When **5a-Me** is compared with the CBS catalyst, the reference reagent for this chemistry, over a set of 8 ketones (**8a**−**c**,**f**−**j**) that have been reduced with both oxazaborolidines, the difference in favor of the CBS reagent between the mean enantiomeric excesses of the resulting alcohols is only 2% (95 vs 93%).

Rationalization of the Observed Enantioselectivity in the Reduction of Prochiral Ketones Mediated by 5a-Me. As we have already discussed, it is widely accepted that oxazaborolidines, through their adjacent boron and nitrogen atoms with complementary Lewis acid and Lewis base character, can give rise to complexes incorporating one borane and one ketone molecule in an arrangement very favorable for reaction. In this process, the role of the substituents at the carbon atoms of the oxazaborolidine ring (those of the starting amino alcohol) is that of directing the complexation of the reactants toward the less hindered diastereotopic face of the oxazaborolidine ring. When a prochiral ketone (R_LCOR_S) is involved in the process, four possible geometries can exist for these complexes (Figure 2) depending on the oxygen lone pair involved in the complexation and the enantiotopic face of the carbonyl compound offered to the BH_3 moiety. In their names, the exo/endo term refers to the value of the dihedral angle $CH_3-B-O=C$ (nearly 0° in exo complexes and nearly 180° in endo ones), whereas *Re*/*Si* refers to the topicity of the face of the carbonyl group *opposite to* the BH_3 moiety.

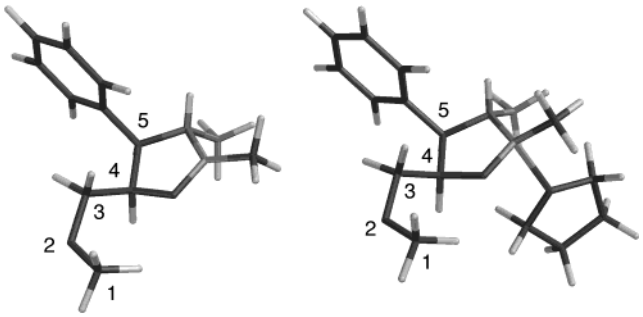
It is interesting to note that, according to the least motion principle, exo complexes must evolve into chair type transition states, whereas endo complexes should correspondingly evolve into boat type ones. For convenience, we have retained for the transition states the same nomenclature employed for the complexes. According to it, *Re* transition states lead to *R* alcohols and *Si* transition states correspondingly lead to *S* alcohols.

Several theoretical studies, involving different levels of theory, have been devoted to this process on both model[15a] and real systems.[15] Whereas Quallich and Blake have reported the highest level ab initio calculations for a model system, Liotta has performed an exhaustive MNDO analysis of the origin of the enantioselectivity with prolinol-based oxazaborolidines.

In any case, the calculated energy differences between the different transition states are so small that all of them should be considered when analyzing the observed enantioselectivity with a new type of oxazaborolidine.

In the present instance, we studied at the AM1 level of theory the possible modes of complexation of 1-phenylethan-1-one and 3,3-dimethylbutan-2-one with the borane adduct of **5a-Me**, as well as the derived transition states, in agreement with the commonly accepted mechanism of the reaction. Whereas for all the studied complexes a complete geometry optimization was performed, in the corresponding transition states the critical B−H−C distances were fixed to the values reported by Quallich for a model system at the ab initio MP2/6-31G(d)//MP2/6-31G(d) level of theory. This finds justification in the fact that geometries optimized at these two levels of theory tend to be similar, since electron correlation is considered (explicitly in the MP2 ab initio calculations and implicitly in the semiempirical ones) in both cases.

As a preliminary step, a conformational analysis of the *N*-BH_3 (**I**) and the *N*-BH_3/*B*-THF (**II**) adducts of oxazaborolidine **5a-Me** was performed. In both cases, the



preferred conformation of the CH_3OCH_2CHCH- fragment turned out to be of the g^+a type, other conformers being at least 2 kcal·mol^{-1} less stable. According to this, g^+a conformers were considered as the starting point for all geometry optimizations in this study.

We have summarized in Table 5 the AM1-calculated heats of formation of the different complexes and transition-state models involving the *N*-BH_3 adduct of oxazaborolidine **5a-Me** and 1-phenylethan-1-one (**8a**) and 3,3-dimethylbutan-2-one (**8f**) as substrate ketones. Relative energies within the different families of complexes and transition-state models are also given, as well as the energy barrier connecting every complex/transition state pair.

If interconversion between complexes is much faster than reaction, the enantioselectivity of the reaction is simply determined, according to the Curtin−Hammett principle,[16] by the energy difference between the most favorable *Re*- and *Si*-type transition states. If this inter-

(15) (a) Quallich, G. J.; Blake, J. F.; Woodall, T. M. *J. Am. Chem. Soc.* **1994**, *116*, 8516−8525. (b) Nevalainen, V. *Tetrahedron: Asymmetry* **1992**, *3*, 1563−1572. (c) Jones, D. K.; Liotta, D. C.; Shinkai, I.; Mathre, D. J. *J. Org. Chem.* **1993**, *58*, 799−801. (d) Nevalainen, V. *Tetrahedron: Asymmetry* **1993**, *4*, 1597−1602. (e) Linney, L. P.; Self, C. R.; Williams, I. H. *J. Chem. Soc., Chem. Commun.* **1994**, 1651−2.

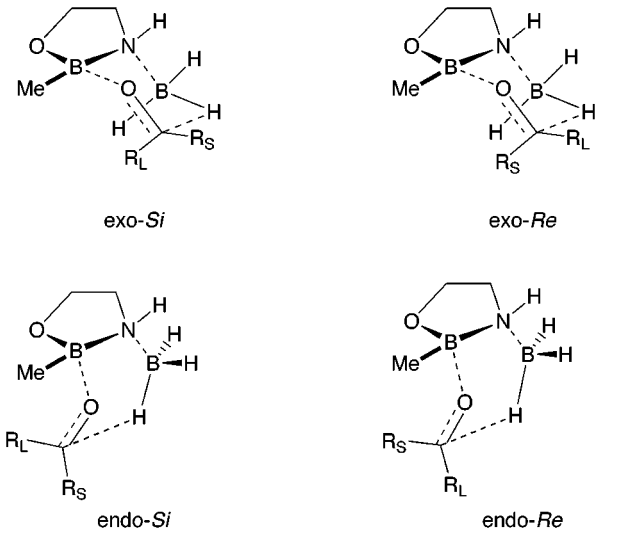


Figure 2. Schematic representation of the four possible reactive complexes and derived transition states in the oxazaborolidine-mediated reduction of a prochiral ketone with borane.

Table 5. AM1-Calculated Heats of Formation[a] of the Reactive Complexes of Oxazaborolidine 5a-Me with Borane and 1-Phenylethan-1-one or 3,3-Dimethylbutan-2-one and of the Corresponding Transition States Leading to Secondary Alcohols

	1-phenylethan-1-one			3,3-dimethylbutan-2-one		
	complex	T.S. model	barrier	complex	T.S. model	barrier
exo-Si	−140.6 (0.0)	−134.8 (0.0)	5.8	−187.5 (0.0)	−181.9 (0.0)	5.6
exo-Re	−138.4 (2.2)	−133.2 (1.6)	5.2			
endo-Si	−137.4 (3.2)	−132.3 (2.5)	5.1			
endo-Re	−138.4 (2.2)	−132.2 (2.6)	6.2	−186.0 (1.5)	−179.6 (2.3)	6.4

[a] All values are in kcal mol^{-1}. Values in parentheses are relative energies within a column.

conversion is to take place through a dissociative process, an estimation of the corresponding barriers could be done through the enthalpy change of the solvent-assisted dissociation represented in Scheme 7. We have summarized in Table 6 the AM1-calculated values for the dissociation of the different complexes of 1-phenylethan-1-one (**8a**) and 3,3-dimethylbutan-2-one (**8f**). Taking into account the nature of the considered processes and the small enthalpy changes predicted by the calculations, it can be deduced that barriers for complex interconversion should also be small.

Barriers for reaction of the different complexes, in turn, are directly available from their heats of formation and those of the corresponding transition states (5.1−6.4 kcal·mol^{-1}, Table 5). Interestingly, they are only slightly higher than those found at the MP2/6-31G(d)//MP2/6-31G(d) level of theory (3.1−4.1 kcal·mol^{-1}) for a reduction of the same type.[15a] A comparison between the data in Tables 5 and 6 indicates as discussed above that complex interconversion should be much faster than the corresponding reduction step. Therefore, the direct comparison between heats of formation of the most favorable transition states of *Re*- and *Si*-type for a given ketone represents a valid approximation to the analysis of the enantioselectivity of the reduction.

Scheme 7

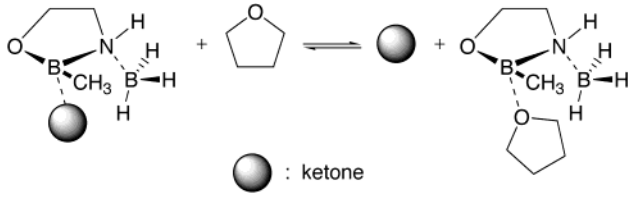


Table 6. Solvent-Assisted Dissociation of the Reactive Complexes of 5a-Me with Borane and 1-Phenylethan-1-one (8a) or 3,3-Dimethylbutan-2-one (8f)

	1-phenylethan-1-one $\Delta H°$ (kcal mol^{-1})	3,3-dimethylbutan-2-one $\Delta H°$ (kcal mol^{-1})
exo-Si	+2.7	+3.4
exo-Re	+0.5	
endo-Si	−0.5	
endo-Re	+0.6	+1.9

According to this, the enantioselectivity in the reduction of 1-phenylethan-1-one arises from the energy difference between the exo-*Si* and the exo-*Re* transition states, the former being preferred by 1.6 kcal·mol^{-1}. In the reduction of 3,3-dimethylbutan-2-one, in turn, the very important steric bulk of the *tert*-butyl substituent precludes the achievement of some of the transition geometries (the exo-*Re* and the exo-*Si* ones, which would present unavoidable steric interactions between the ketone and the oxazaborolidine moieties). In this case, enantioselectivity in the reaction seems to obey to the energy difference between the exo-*Si* and the endo-*Re* transition states, the former being preferred by 2.3 kcal·mol^{-1}. A representation of the relevant transition states in the reduction of the ketones discussed above can be found in Figure 3.

The theoretical calculations reported here predict that the reduction with borane of prochiral ketones mediated by oxazaborolidine **5a-Me** will preferentially lead to alcohols of *S* configuration, as is experimentally observed.[17] Again, in agreement with experimental observation, it is predicted that the reduction of 3,3-dimethylbutan-2-one at room temperature will take place with higher enantioselectivity than that of 1-phenylethan-1-one. Moreover, the present calculations could also provide a clue on the capricious enantioselectivity/temperature dependence observed in the reduction of the ketones in this paper. Thus, it is well-known that the occurrence of a nonlinear dependence between enantioselectivity and temperature obeys to some kind of mechanism change in the process.[18] In processes where every component of a product stereoisomeric mixture can be formed through two or more transition states, a simple variation with temperature of the preference for the different reaction modes (as a consequence of, for instance, their different activation entropies) would be a sufficient condition for the observation of a nonlinear behavior. The possibility of attaining all four possible transition states in the

(16) (a) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 3rd ed.; Plenum Press: New York, 1990; pp 215−216. (b) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; pp 647−655.

(17) The priority order of the substituents in the reduction product of **8b** accounts for the *R* configuration of the final compound.

(18) Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 477−515.

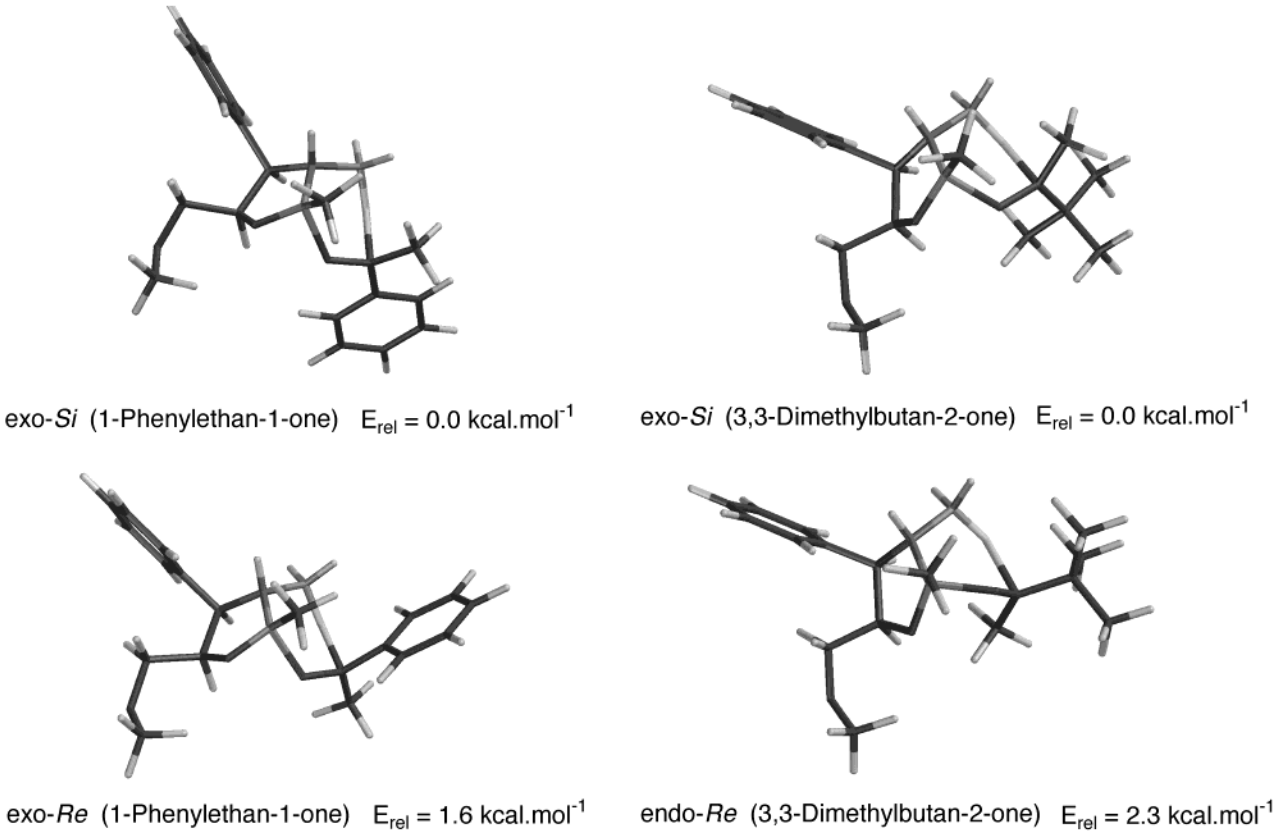


Figure 3. Representation of the relevant transition states (AM1) in the reduction of 1-phenylethan-1-one (**8a**) and 3,3-dimethylbutan-2-one (**8f**).

reduction of prochiral ketones not containing a too bulky substituent, as seen for 1-phenylethan-1-one (see also ref 15c) opens the way for such behavior.

Conclusions

In summary, the synthesis of chiral oxazaborolidines from enantiomerically pure (2*S*,3*S*)-2,3-epoxy-3-phenylpropanol has led to the development of a new family of catalysts for the enantioselective reduction of ketones. Thanks to the modular design of the target molecules, some of their structural elements have been optimized with great ease for improved enantioselectivity. As a result, (4*R*,5*R*)-2-methyl-4-phenyl-5-methoxymethyl-1,3,2-oxazaborolidine (**5a-Me**) has been developed as a new mediator for the enantioselective reduction of prochiral ketones with interesting characteristics: It can be used in most cases at room temperature and the enantiomeric excess of the resulting alcohols approaches that obtained with the CBS reagent (2% difference in mean ee over a family of 8 ketones). As indicated by semiempirical AM1 calculations the observed enantioselectivity arises, within the framework of the commonly accepted mechanism for these reactions, from the preference for a chairlike transition state with the hydride being transferred from boron to the *Re* face of the reacting ketone.

Experimental Section

General Methods. ^{1}H NMR and ^{13}C NMR spectra in solution were recorded in $CDCl_3$ at 200 and 50 MHz, respectively, unless otherwise cited. ^{1}H chemical shifts are quoted relative to TMS and ^{13}C chemical shifts relative to solvent signals. Elemental analyses were carried out by the Servei d'Anàlisi Elementals del CSIC de Barcelona. High-resolution mass spectra (CI) were measured by the Servicio de Espectrometría de Masas de la Universidad de Córdoba. Chromatographic separations were carried out using NEt_3-pretreated (2.5% v/v) SiO_2 (70−230 mesh). THF was freshly distilled from benzophenone ketyl under N_2. 2-Iodo-1-methoxyethane and 2-iodo-1-(2-methoxyethoxy)ethane[19] were prepared as described in the literature. (2*S*,3*S*)-2,3-Epoxy-3-phenylpropanol, **2**, was prepared according to the procedure described by Sharpless et al.[20]

1-[((2*S*,3*S*)-3-Phenyloxiran-2-yl)methoxy]-2-methoxyethane, 7b. A solution of **2** (3.00 g, 20 mmol) in DMF (24 mL) was added *via cannula* to a suspension of sodium hydride (3.60 g, ca. 120 mmol) in DMF (24 mL) at 0 °C under N_2. The mixture was stirred for 20 min, and 2-iodo-1-methoxyethane (22.30 g, 120 mmol) was added via syringe into the mixture. The mixture was stirred for 15 h at 0 °C. MeOH (250 mL) and brine (250 mL) were added. The aqueous solution was extracted with Et_2O. The combined organic extracts were dried and concentrated in vacuo. The residual oil was chromatographed using hexane/EtOAc (95:5) as eluent to give 3.27 g (79%) of **7b** as an oil: $[\alpha]^{23}_D = -36.1$ (c = 1.1 in $CHCl_3$); ^{1}H NMR δ 7.19−7.38 (m, 5H), 3.89 (dd, J = 11.7, 2.9 Hz, 1H), 3.79 (d, J = 2.2 Hz, 1H), 3.55−3.75 (m, 5H), 3.40 (s, 3H), 3.24 (ddd, J = 5.3, 3.1, 2.2 Hz, 1H); ^{13}C NMR δ 136.7 (C), 128.3 (CH), 128.1 (CH), 125.6 (CH), 71.8 (CH_2), 71.0 (CH_2), 70.7 (CH_2), 61.0 (CH), 58.9 (CH_3), 55.7 (CH); IR (film) 2881, 1200, 1109 cm^{-1}; MS (CI, CH_4) m/z 209 ($C_{12}H_{16}O_3$·H$^+$, 100); HRMS (CI, CH_4) for $C_{12}H_{16}O_3$ (M^+) 208.1099, found 208.1088.

1-[((2*S*,3*S*)-3-Phenyloxiran-2-yl)methoxy]-2-(2-methoxyethoxy)ethane, 7c. Compound **2** (0.52 g, 3.4 mmol) in

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DMF (7 mL), sodium hydride (1.19 g, ca. 40 mmol) in DMF (9 mL), and 2-iodo-1-(2-methoxyethoxy)ethane (7.93 g, 34 mmol) were treated as described for **7b** with stirring 24 h at 0 °C to give 820 mg (95%) of **7c** as an oil after chromatography using hexane/EtOAc (100:0/90:10): $[\alpha]^{23}_D = -30.5$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (500 MHz) δ 7.27−7.32 (m, 5H), 3.87 (dd, $J = 11.6$, 3.5 Hz, 1H), 3.78 (d, $J = 2.0$ Hz, 1H), 3.63 (dd, $J = 11.6$, 5.0 Hz, 1H), 3.54−3.77 (m, 8H), 3.37 (s, 3H), 3.20 (ddd, $J = 5.0$, 3.5, 2.0 Hz, 1H); ^{13}C NMR δ 136.8 (C), 128.4 (CH), 128.1 (CH), 125.6 (CH), 71.8 (CH_2), 70.9 (CH_2), 70.6 (CH_2), 70.52 (CH_2), 70.47 (CH_2), 61.0 (CH), 58.9 (CH_3), 55.7 (CH); IR (film) 2877, 1104 cm^{-1}; MS(CI, NH_3) m/z 270 ($C_{14}H_{20}O_4 \cdot NH_4^+$, 100) and 253 ($C_{14}H_{20}O_4 \cdot H^+$, 3); HRMS(CI, CH_4) for $C_{14}H_{21}O_4$ ($M + H^+$) 253.1440, found 253.1417.

General Procedure for the Regioselective Oxirane Ring Opening Followed by Hydrogenation of the Azido Group: (1*R*,2*R*)-1-Amino-3-methoxy-1-phenylpropan-2-ol, 4a. A solution of **7a** (4.90 g, 30 mmol), $LiClO_4$ (78.40 g, 737 mmol), and NaN_3 (9.70 g, 149 mmol) in acetonitrile (147 mL) was stirred at 55 °C for 24 h under N_2. H_2O (1.8 L) was added, and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried and concentrated in vacuo to give 6.17 g of **6a** as an oil that was used in the next step without further purification. A solution of **6a** (6.17 g, 29.8 mmol) in MeOH (75 mL) was added via syringe to a suspension of Pd/C 10% (0.62 g) in MeOH (108 mL) at room temperature under H_2. After 36 h of stirring at this temperature, the mixture was filtered through Celite. The residual oil was chromatographed through a short SiO_2 column using hexane/EtOAc (50:50) as eluent to give 4.9 g (91%) of **4a** as an oil: $[\alpha]^{23}_D = -31.2$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR δ 7.37−7.26 (m, 5H), 4.14 (d, 1H, $J = 5.2$ Hz), 3.93 (ddd, $J = 5.2$, 5.2, 5.2 Hz, 1H), 3.32−3.34 (m, 2H), 3.33 (s, 3H), 2.09 (br s, 3H, NH_2 + OH);^{13}C NMR δ 142.0 (C), 128.4 (CH), 127.4 (CH), 127.1 (CH), 73.6 (CH_2), 73.2 (CH), 59.1 (CH_3), 57.8 (CH); IR (film) 3361, 3298 cm^{-1}; MS (CI, NH_3) m/z 199 ($C_{10}H_{15}NO_2 \cdot NH_4^+$, 20) and 182 ($C_{10}H_{15}NO_2 \cdot H^+$, 100). Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 65.93; H, 8.19; N, 7.37.

(1*R*,2*R*)-1-Amino-3-(2-methoxyethoxy)-1-phenylpropan-2-ol, 4b. Compound **7b** (1.10 g, 5 mmol), $LiClO_4$ (13.90 g, 130 mmol), and NaN_3 (1.76 g, 27 mmol) in acetonitrile (27.1 mL) were treated as described for **7a** during 24 h. The workup was identical to the one described for **7a** to give 1.30 g of **6b** as an oil that was used in the next step without further purification. A solution of **6b** (1.30 g, 5 mmol) in MeOH (13 mL) was added via syringe to a suspension of Pd/C 10% (0.13 g) in MeOH (18.7 mL) at room temperature under H_2. After 15 h of stirring at this temperature, the mixture was filtered through Celite. The residual oil was chromatographed through a short SiO_2 column using hexane/EtOAc (30:70) as eluent to give 0.98 g (84%) of **4b** as an oil: $[\alpha]^{23}_D = -31.7$ ($c = 1.3$ in $CHCl_3$); ^{1}H NMR δ 7.36−7.27 (m, 5H), 4.13 (d, $J = 5.0$ Hz, 1H), 3.97 (ddd, $J = 5.2$, 5.2, 5.2 Hz, 1H), 3.60−3.48 (m, 4H), 3.43−3.40 (m, 2H), 3.36 (s, 3H), 2.33 (br s, 3H, NH_2 + OH);^{13}C NMR δ 142.1 (C), 128.3 (CH), 127.2 (CH), 127.1 (CH), 73.5 (CH), 72.2 (CH_2), 71.7 (CH_2), 70.4 (CH_2), 58.9 (CH_3), 57.8 (CH); IR (film) 3365, 3298, 1104 cm^{-1}; MS (CI, CH_4) m/z 226 ($C_{12}H_{19}NO_3 \cdot H^+$, 100); HRMS (CI) calcd for $C_{12}H_{19}NO_3 \cdot H^+$ 226.1443, found 226.1434.

(1*R*,2*R*)-1-Amino-3-[2-(2-methoxyethoxy)ethoxy]-1-phenylpropan-2-ol, 4c. Compound **7c** (1.00 g, 4 mmol), $LiClO_4$ (10.40 g, 98 mmol), and NaN_3 (1.30 g, 20 mmol) in acetonitrile (19.8 mL) were treated as described for **7a** during 24 h. The workup was identical to the one described for **7a** to give 1.17 g of **6c** as an oil that was used in the next step without further purification. A solution of **6c** (1.17 g, 4 mmol) in MeOH (10 mL) was added via syringe to a suspension of Pd/C 10% (0.12 g) in MeOH (20 mL) at room temperature under H_2. After 36 h of stirring at this temperature, the mixture was filtered through Celite. The residual oil was chromatographed through a short SiO_2 column using hexane/EtOAc (30:70) as eluent to give 0.86 g (81%) of **4c** as an oil: $[\alpha]^{23}_D = -28.5$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR δ 7.36−7.23 (m, 5H), 4.15 (d, $J = 5.2$ Hz, 1H), 3.97 (ddd, $J = 5.2$, 5.2, 5.2 Hz, 1H), 3.64−3.53 (m, 8H), 3.43−3.41 (m, 2H), 3.37 (s, 3H), 2.61 (br s, 3H, NH_2 + OH);^{13}C NMR δ 142.0 (C), 128.3 (CH), 127.9 (CH), 127.3 (CH), 127.1 (CH), 73.5 (CH), 72.1 (CH_2), 71.8 (CH_2), 70.5 (CH_2), 70.4 (CH_2), 59.0 (CH_3), 57.8 (CH); IR (film) 3367, 1109 cm^{-1}; MS (CI, NH_3) m/z 270 ($C_{14}H_{23}NO_4 \cdot H^+$, 100); HRMS (CI) calcd for $C_{14}H_{23}NO_4 \cdot H^+$ 270.1705, found 270.1710.

General Procedure for the Regioselective Oxirane Ring Opening Followed by Reduction of the Azido Group with $NaBH_4$: (1*R*,2*R*)-1-Amino-1-phenyl-3-(phenylmethoxy)propan-2-ol, 4d. Compound **7d** (3.20 g, 13 mmol), $LiClO_4$ (34.90 g, 328 mmol), and NaN_3 (4.30 g, 66 mmol) in acetonitrile (66 mL) were treated as described for **7a** during 24 h. The workup was identical to the one described for **7a** to give 3.76 g of **6d** as an oil that was used in the next step without further purification. A solution of **6d** (3.76 g, 13 mmol) and sodium borohydride (1.60 g, 42 mmol) in THF (30.4 mL) was heated at 55−60 °C under N_2. MeOH (6.6 mL) was added during 1 h. After the mixture was heated at this temperature for 16 h, H_2O (560 mL) was added, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated in vacuo. The residual oil was chromatographed through a short SiO_2 column using hexane/EtOAc (80:20−60:40) as eluent to give 3.14 g (92%) of **4d** as a colorless oil: $[\alpha]^{23}_D = -21.8$ ($c = 0.9$ in $CHCl_3$); ^{1}H NMR δ 7.38−7.25 (m, 10H), 4.48 (s, 2H), 4.16 (d, $J = 5.2$ Hz, 1H), 3.97 (ddd, $J = 5.2$, 5.2, 5.2 Hz, 1H), 3.44−3.46 (m, 2H), 2.07 (br s, 3H, NH_2 + OH);^{13}C NMR δ 141.8 (C), 137.8 (C), 128.3 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.2 (CH), 127.1 (CH), 73.3 (CH), 73.3 (CH_2), 71.4 (CH_2), 57.7 (CH); IR (film) 3363, 1102, 1073 cm^{-1}; MS (CI, NH_3) m/z 275 ($C_{16}H_{19}NO_2 \cdot NH_4^+$, 4) and 258 ($C_{16}H_{19}NO_2 \cdot H^+$, 100); HRMS (CI) calcd for $C_{16}H_{19}NO_2 \cdot H^+$ 258.1494, found 258.1504.

(1*R*,2*R*)-1-Amino-1-phenyl-3-(diphenylmethoxy)propan-2-ol, 4e. Compound **7e** (0.20 g, 0.6 mmol), $LiClO_4$ (1.65 g, 15 mmol), and NaN_3 (0.20 g, 3 mmol) in acetonitrile (3.1 mL) were treated as described for **7a** during 24 h. The workup was identical to the one described for **7a** to give 0.23 g of **6e** as an oil that was used in the next step without further purification. A solution of **6e** (0.23 g, 0.6 mmol) and sodium borohydride (77 mg, 2 mmol) in THF (1.5 mL) was heated at 55−60 °C under N_2. MeOH (0.32 mL) was added during 1 h, and the mixture was heated at this temperature for 7 h. A workup identical to the one described for **4d** followed by chromatography through a short SiO_2 column using hexane/EtOAc (60:40) as eluent yielded 0.15 g (73%) of **4e** as a white solid that was recrystallized from MeOH to obtain an analytically pure sample: mp 125−7 °C; $[\alpha]^{23}_D = -21.5$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.31−7.19 (m, 15H), 5.27 (s, 1H), 4.13 (d, $J = 4.8$ Hz, 1H), 4.00 (ddd, $J = 4.8$, 4.8, 4.8 Hz, 1H), 3.39−3.41 (m, 2H), 2.57 (br s, 3H, NH_2 + OH); ^{13}C NMR (75 MHz) δ 141.9 (C), 128.5 (CH), 128.4 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 127.2 (CH), 127.1 (CH), 127.0 (CH), 126.9 (CH), 84.3 (CH), 73.6 (CH), 70.3 (CH_2), 58.0 (CH); IR (film) 3357, 1075 cm^{-1}; MS (CI, NH_3) m/z 351 ($C_{22}H_{23}NO_2 \cdot NH_4^+$, 5) and 334 ($C_{22}H_{23}NO_2 \cdot H^+$, 100). Anal. Calcd for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20. Found: C, 79.10; H, 7.02; N, 4.16.

(1*R*,2*R*)-1-Amino-1-phenyl-3-(triphenylmethoxy)propan-2-ol, 4f. Compound **7f** (2.30 g, 6 mmol), $LiClO_4$ (15.40 g, 145 mmol), and NaN_3 (1.90 g, 29 mmol) in acetonitrile (29.3 mL) were treated as described for **7a** during 24 h. The workup was identical to the one described for **7a** to give 2.60 g of **6f** as an oil that was used in the next step without further purification. A solution of **6f** (2.60 g, 6 mmol) and sodium borohydride (0.72 g, 19 mmol) in THF (13.7 mL) was heated at 55−60 °C under N_2. MeOH (3 mL) was added during 1 h, and the mixture was heated at this temperature for 22 h. A workup identical to the one described for **4d** followed by chromatography through a short SiO_2 column using hexane/EtOAc (60:40) as the eluent yielded 2.13 g (87%) of **4f** as a white solid that was recrystallized from Et_2O to obtain an analytically pure sample: mp 57−58 °C; $[\alpha]^{23}_D = -22.6$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.43−7.18 (m, 20H), 4.17 (d, $J = 5.1$ Hz, 1H), 3.91 (ddd, $J = 5.1$, 5.1, 5.1 Hz, 1H), 3.15−3.06 (m, 2H), 2.24 (br s, 3H, NH_2 + OH);^{13}C NMR (50 MHz) δ 143.7 (C), 141.8 (C), 128.6 (CH), 128.3 (CH), 127.8 (CH), 127.6 (CH), 127.2 (CH), 127.0 (CH), 86.8 (C), 73.9 (CH), 64.4 (CH_2), 58.1 (CH); IR (film) 3363, 1067 cm^{-1}; MS (CI) m/z 427 ($C_{28}H_{27}NO_2 \cdot NH_4^+$, 2) and 410 ($C_{28}H_{27}$-

$NO_2 \cdot H^+$, 50). Anal. Calcd for $C_{28}H_{27}NO_2$: C, 82.12; H, 6.65; N, 3.42. Found: C, 81.75; H, 6.79; N, 3.29.

General Procedure for the Reduction of Prochiral Ketones 8a,b Using (4*R*,5*R*)-4-Phenyl-5-(R¹-oxymethyl)-1,3,2-oxazaborolidines (5a-H, 5b-H, 5c-H, 5d-H, 5e-H, and 5f-H) as Chiral Catalysts. Borane−methyl sulfide complex (66 μL of a 10 M BH_3 solution in Me_2S, 0.7 mmol) was added via syringe to a solution of the amino alcohol (0.055 mmol, 10 mol %) in THF (1.5 mL) at room temperature under N_2. The mixture was stirred at this temperature for 16 h, and a solution of the ketone (0.55 mmol) in THF (0.7 mL) was added dropwise with the aid of a syringe pump over a 1 h period. The mixture was further stirred for 10 min under N_2. The reaction was quenched by the addition of a 2 M HCl solution (2 mL) and the mixture extracted with Et_2O. The combined organic extracts were dried and concentrated in vacuo. The enantiomeric excesses were determined from the crude mixture by GC analyses. For the conditions of the GC analyses and the determination of the absolute configuration of the final compounds, see below.

General Procedure for the Reduction of Prochiral Ketones Using (4*R*,5*R*)-2-Methyl-4-phenyl-5-(R¹-oxymethyl)-1,3,2-oxazaborolidines (5a-Me, 5b-Me, 5c-Me, 5d-Me, 5e-Me, and 5f-Me) as Chiral Catalysts. (a) Preparation of the *B*-Me Oxazaborolidines. Trimethylboroxine (0.21 mL, 1.5 mmol) was added via syringe to a solution of the amino alcohol **4a**−**f** (2.2 mmol) in toluene (14.4 mL), and the mixture was stirred under N_2 at room temperature for 1 h. Toluene, excess trimethylboroxine, and water were distilled off at atmospheric pressure until ca. 4 mL remained. The mixture was diluted with toluene (3 × 7 mL), each time distilling until ca. 4 mL was left. Toluene (0.4 mL) was then added to provide a 0.5 M solution of the *B*-methyl oxazaborolidines in toluene. **(b) Catalytic Enantioselective Reduction of Prochiral Ketones 8a**−**j.** The corresponding *B*-Me oxazaborolidine **5-Me** (78 μL of a 0.5 M solution in toluene, 0.039 mmol, 10%) together with 1.1 mL of THF was introduced via syringe into a flame-dried flask under N_2. Borane−methyl sulfide complex (47 μL of a 10 M BH_3 solution in Me_2S, 0.47 mmol) was added via syringe to the previous solution. The mixture was heated or cooled to the desired temperature if necessary. A solution of the ketone (0.39 mmol) in THF (0.5 mL) was added dropwise with the aid of a syringe pump over a 1 h period. The mixture was further stirred for 10 min at the appropriate temperature under N_2. The reaction was quenched by the addition of a 2 M HCl solution (2 mL) and the mixture extracted with Et_2O. The combined organic extracts were dried and concentrated in vacuo. The enantiomeric excesses were determined from the crude mixture by GC analyses. Conditions of GC analyses: β-DEX 120 or α-DEX 120 column, 30 m length, 0.25 mm internal diameter, isotherm temperature program, He as carrier gas (2.4 mL/min). For 1-phenylethan-1-ol: β-DEX 120, 100 °C, t_R *R* isomer 52.1 min, t_R *S* isomer 55.7 min. For 2-chloro-1-phenylethan-1-ol: β-DEX 120, 125 °C, t_R *S* isomer 70.1 min, t_R *R* isomer 73.8 min. For 1-(3-methoxyphenyl)ethan-1-ol: β-DEX 120, 122 °C, t_R *R* isomer 78.4 min, t_R *S* isomer 82.3 min. For 1-(3-chlorophenyl)-ethan-1-ol: β-DEX 120, 125 °C, t_R *R* isomer 57.7 min, t_R *S* isomer 61.1 min. For 1-(4-chlorophenyl)ethan-1-ol: β-DEX 120, 125 °C, t_R *R* isomer 60.6 min, t_R *S* isomer 65.8 min. For 1-(2-methoxyphenyl)ethan-1-ol: β-DEX 120, 122 °C, t_R *S* isomer 58.6 min, t_R *R* isomer 64.0 min. For 1-phenylpropan-1-ol: β-DEX 120, 112 °C, t_R *R* isomer 47.4 min, t_R *S* isomer 49.1 min. For 1,2,3,4-tetrahydronaphthol: β-DEX 120, 125 °C, t_R *S* isomer 89.2 min, t_R *R* isomer 93.3 min. For 3,3-dimethylbutan-2-ol: β-DEX 120, 70 °C, t_R *R* isomer 14.7 min, t_R *S* isomer 15.0 min. For 1-cyclohexylethan-1-ol: α-DEX 120, 70 °C, t_R *R* isomer 67.6 min, t_R *S* isomer 69.5 min.

To stablish the absolute configuration of the final compounds, the alcohols were purified by bulb-to-bulb distillation of the crude mixtures. The optical rotation was measured in each case and its sign was compared with the reported value ((*1S*)-1-phenylethan-1-ol,[21a] (*1R*)-2-chloro-1-phenylethan-1-ol,[21b] (*1S*)-1-(3-methoxyphenyl)ethan-1-ol,[21c] (*1S*)-1-(4-chlorophenyl)ethan-1-ol,[21d] (*1S*)-1-(2-methoxyphenyl)ethan-1-ol,[21e] (*1S*)-1-phenylpropan-1-ol,[21f] (*1S*)-1,2,3,4-tetrahydronaphthol,[21a] (*1S*)-1-cyclohexylethan-1-ol,[21g] and 3,3-dimethylbutan-2-ol[21g]).

General Procedure for the Reduction of Prochiral Ketones Using (4*R*,5*R*)-2-Butyl-4-phenyl(1,3,2-oxazaborolidin-5-yl)methoxymethane (5a-Bu) as the Chiral Catalyst. (a) Preparation of the *B*-Bu Oxazaborolidine 5a-Bu. Butylboronic acid (62 mg, 0.605 mmol) was added to a solution of the amino alcohol **4a** (0.1 g, 0.55 mmol) in toluene (7 mL) in a round-bottom flask fitted with a Dean−Stark apparatus and a reflux condenser. The reaction mixture was stirred under N_2 at room temperature for 0.5 h and then refluxed for 16 h. The solvent was distilled off until ca. 1 mL was left. Toluene (0.1 mL) was then added to provide a 0.5 M solution of catalyst. **(b) Catalytic Enantioselective Reduction of Prochiral Ketones 8a,b.** The chiral catalyst **5a-Bu** (78 μL of a 0.5 M solution in toluene, 0.039 mmol, 10%) together with 1.1 mL of THF were introduced via syringe into a flame-dried flask under N_2. Borane−methyl sulfide complex (47 μL of a 10 M BH_3 solution in Me_2S, 0.47 mmol) was added via syringe to the previous solution. A solution of the ketone (0.39 mmol) in THF (0.5 mL) was added dropwise with the aid of a syringe pump over a 1 h period. The mixture was further stirred for 10 min under N_2. The reaction was quenched by the addition of a 2 N HCl solution (2 mL) and the mixture extracted with Et_2O (3 × 2 mL). The combined organic extracts were dried and concentrated in vacuo. The enantiomeric excesses were determined from the crude mixture by GC analyses. For the conditions of the GC analyses and the determination of the absolute configuration of the final compounds see above.

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