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Chiral oxazaborolidines bearing a 1- or 2-naphthylmethyl group as catalysts for the enantioselective borane reduction of ketones: experimental and quantum chemical calculations

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Abstract

Two new catalysts for the enantioselective reduction of ketones, chiral 1,3,2-oxazaborolidines substituted at carbon 4 by a 1- or 2-naphthylmethyl group, have been prepared from the related amino alcohols, by treatment with borane in tetrahydrofuran, and the effectiveness of these two catalysts has been investigated. The stereochemical outcomes were verified by means of quantum calculations using the AM1 computational method. © 1998 Published by Elsevier Science Ltd. All rights reserved.

Chiral 1,3,2-oxazaborolidine catalysts have been successfully employed for the asymmetric borane reduction of ketones in recent years.[1] Many new catalysts, derived from natural or unnatural starting materials, have been prepared in order to find more effective and economic catalysts.[1] At the same time, a number of papers on structure–enantioselectivity relationships of the catalyst have been published.[2] Some papers on quantum chemical research in this field have appeared,[3] after Corey had suggested their mechanism for this reduction.[4]

According to Corey, the borane reduction of prochiral ketones using chiral 1,3,2-oxazaborolidines as catalysts consists of four steps: I, formation of the borane adduct **3**; II, coordination of the ketone to be reduced to borane adduct **3** forming **4**; III, stereospecific transformation of a hydride from BH_3 to the carbonyl carbon; IV, release of the product regenerating the catalyst.

It has been indicated that to achieve high enantioselectivity in the asymmetric borane reduction, one face of the oxazaborolidine should be totally blocked. In order to verify the above hypothesis, we prepared two new chiral oxazaborolidine catalysts bearing a 1- or 2-naphthylmethyl group at position 4 (**2a** and **2b**), from the (*R*)-β-amino alcohols **1a** and **1b** in situ, by treatment with borane. Then the effectiveness of these two catalysts was investigated through the reduction of a series of prochiral ketones. The reason for the choice of 1- and 2-naphthylmethyl as the substituents is that they are similar in electronic nature

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Table 1
Asymmetric reduction of prochiral ketones with **2a/2b** (0.05 equiv.) and borane (1 equiv.)

Entry	Ketone	Yield (%)[a]		E.e. (%)[b]		Config.[c]
		Cat. 2a	Cat.2b	Cat.2a	Cat. 2b	
1	$C_6H_5COCH_3$	88.7	83.6	76.6	68.2	*S*
2	$C_6H_5COCH_2CH_3$	93.4	86.8	81.3	64.9	*S*
3	$C_6H_5COC_3H_7$-*n*	88.3	90.9	100	58.6	*S*
4	$C_6H_5COC_4H_9$-*n*	91.2	92.1	100	75.8	*S*
5	$CH_3COC_6H_4Cl$-*p*	91.7	84.7	89.9	79.2	*S*
6	$CH_3CO\ C_6H_4\ CH_3$-*p*	86.3	91.2	100	92.0	*S*
7	$CH_3COC_6H_4OCH_3$-*p*	92.2	85.5	100	100	*S*
8	$CH_3COC_4H_9$-*i*	89.7	89.4	72.2	59.5	*S*
9	$CH_3COC_4H_9$-*t*	88.6	89.0	59.1	59.0	*S*

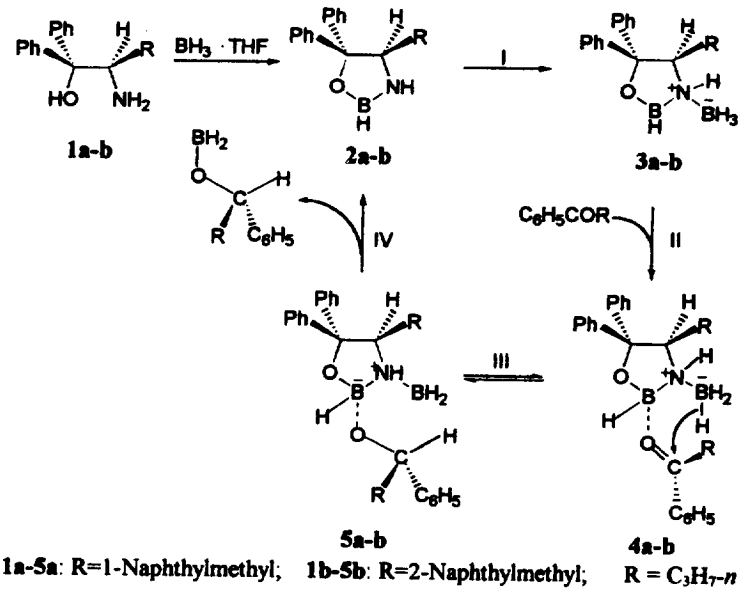
a. Isolated yield. b. Ee's were determined by GC on a chiral capillary column β-DEX120. c. Absolute configuration was assigned by from the sign of the specific rotation.

while the 1-naphthylmethyl group is more bulky than the 2-naphthylmethyl group and hence the catalyst **2a** may be the better one of the two.

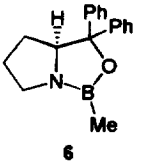
The syntheses of the chiral β-amino alcohols **1a** and **1b** were achieved using a procedure similar to that described in the literature.[5] The structures of **1a** and **1b** were confirmed by elemental analyses, ^{1}H NMR and IR.[6] The borane reduction of prochiral ketones catalyzed by the in situ formed oxazaborolidines **2a** and **2b** was performed as described before,[5] using 0.05 equiv. of **1a** or **1b** and 1 equiv. of borane in THF at 30°C. The results are summerized in Table 1. It was shown that both **2a** and **2b** have high abilities to induce chirality in the product secondary alcohol molecules for the tested ketones, including aralkyl, alkyl and halogen-containing ketones. In particular, excellent results were obtained in the reduction of *p*-methylacetophenone and *p*-methoxyacetophenone when **2a** was employed as the chiral catalyst. These two ketones were reduced to the corresponding secondary alcohols in 100% e.e. Obviously, catalyst **2a** displayed higher stereoselectivity than catalyst **2b**, which is different from **2a** only in the substitution position of the naphthyl group. These results are in accordance with expectation.

Experimental results have been verified by quantum chemical calculations. Energy calculations were made for each of the four steps shown in Scheme 1 by means of the computational AM1 method, using the reduction of butyrophenone with borane and catalyst **2a** or **2b** as the models. The optimized structures **4a**, **4b**, **5a** and **5b** are shown in Fig. 1. In **4a** and **4b**, the catalyst is coordinated to the carbonyl lone pair which is *syn* to the propyl group and *anti* to the phenyl group, leading to the formation of (*S*)-secondary alcohol. The total energy and heat of formation of each optimized structure was summerized in Table 2, and the enthalpies of each step are shown in Table 3.

One can see from the data in Table 3 that both steps I and III are exothermic reactions, while steps II and IV are endothermic. The release of the reduction product from **5** regenerating the catalyst (step IV, the most endothermic step) may be rate-determining. This is in accordance with the experimental results reported by Corey, who had demonstrated, in the borane reduction of acetophenone and its derivatives using **6** as a catalyst, that neither ketone–catalyst coordination nor hydride transfer to carbonyl steps are rate-limiting.[7] By comparing the enthalpies of the pairs IIa/IIb and IVa/IVb, one would find that the formation of complex **4a** is more favorable than the formation of **4b**, and the release of the product regenerating the catalyst from **5a** is more readily accomplished than from **5b**. In conclusion, catalyst **2a** is more effective than catalyst **2b**.



Scheme 1. The mechanism of the oxazaborolidine catalyzed enantioselective borane reduction of ketones



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6. (*R*)-2-Amino-3-(1-naphthyl)-1,1-diphenyl-1-propanol **1a**, recrystallized from ethanol, m.p. 96–97°C, $[\alpha]_D^{25}$ +135 (c=1 in $CHCl_3$). Elemental anal. calcd for $C_{25}H_{23}NO$: C, 84.95; H, 6.56; N, 3.96; found: C, 84.80; H, 6.56; N, 4.00. ^1H NMR (δ ppm, $CDCl_3$): 0.93–1.82 (b, 2H), 2.85 (dd, 1H), 3.10 (dd, 1H), 4.30 (dd, 1H), 4.69–4.80 (b, 1H), 7.04–7.54 (m, 10H), 7.56–7.98 (m, 7H). (*R*)-2-Amino-3-(2-naphthyl)-1,1-diphenyl-1-propanol **1b**, recrystallized from ethanol, m.p. 148–149°C,

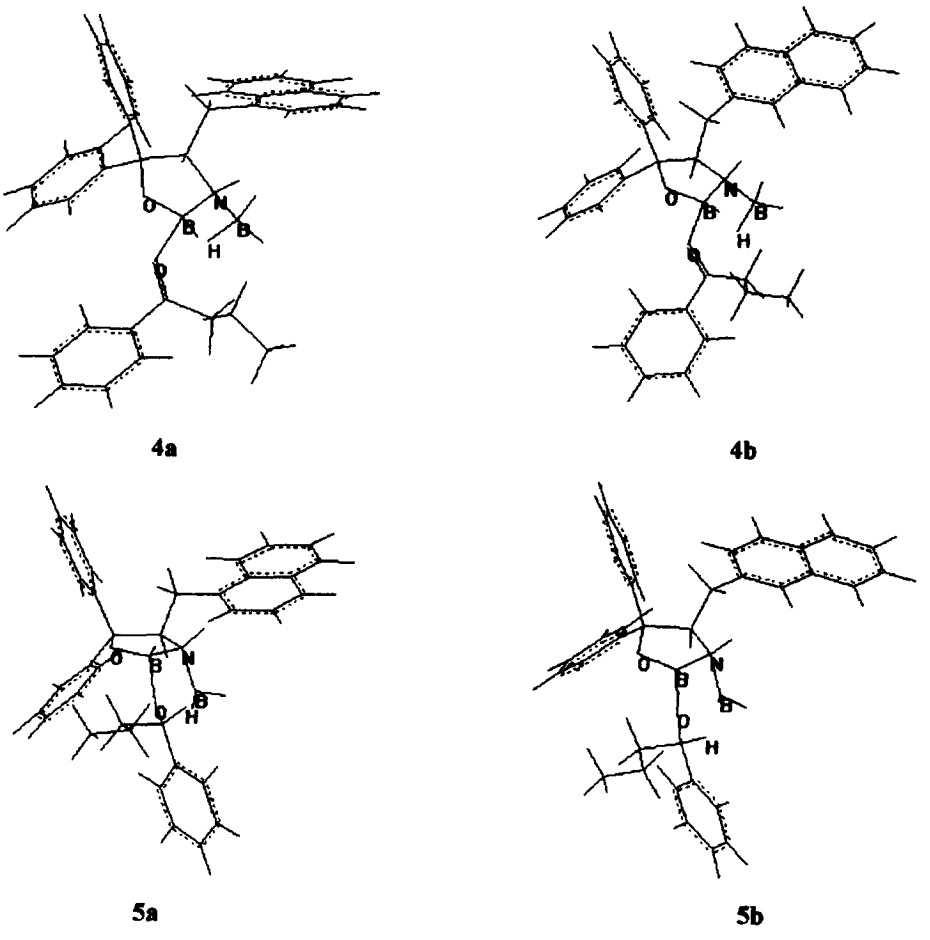

Fig. 1. The optimized structures of **4a**, **4b**, **5a** and **5b**

Table 2
Energies of optimized structures (kJ mol^{-1})

Structure	Total energy E (kJ/mol)	Heat of formation ΔH (kJ/mol)
Borane	-10565.7664	109.7078
Butyrophenone	-170398.8932	-117.2866
4-(1-Naphthylmethyl)-1,3,2-oxazaborolidine 2a	-395901.8792	121.4936
4-(2-Naphthylmethyl)-1,3,2-oxazaborolidine 2b	-395891.3485	132.0243
Catalyst-BH_3 (3a)	-406593.7064	105.1405
Catalyst-BH_3 (3b)	-406619.7681	79.0789
Catalytic complex 4a	-576711.5791	-3.1129
Catalytic complex 4b	-576727.2022	-18.7360
Catalyst-reduction product 5a	-576888.3073	-179.8411
Catalyst-reduction product 5b	-576883.4003	-174.9342
$PhCH(C_3H_7\text{-}n)O\text{-}BH_2$	-181172.1293	-222.1880

Table 3
Enthalpies of each reaction step

	Cat. 2a	Cat. 2b
Step I	-126.0609 kJ/mol	-162.6532 kJ/mol
Step II	9.0332 kJ/mol	19.4717 kJ/mol
Step III	-176.7282 kJ/mol	-156.1982 kJ/mol
Step IV	74.2398 kJ/mol	84.7705 kJ/mol

$[\alpha]_D^{25}$ +49.5 (c=1 in $CHCl_3$). Elemental anal. calcd for $C_{25}H_{23}NO$: C, 84.95; H, 6.56; N, 3.96; found: C, 84.86; H, 6.43; N, 3.95. ^1H NMR (δ ppm, $CDCl_3$): 1.17–1.25 (b, 2H), 2.62–2.84 (m, 2H), 4.21–4.30 (m, 1H), 4.59–4.69 (b, 1H), 7.22–7.48 (m, 10H), 7.65–7.83 (m, 7H).

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