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Asymmetric reduction of aromatic ketones: importance of the conformation of the aromatic group

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Abstract

Some aromatic ketones have been reduced by borane or by catecholborane using oxazaborolidine as a catalyst. It has been found that, when borane is used, the enantiomeric excess of alcohol produced decreases as the substitution on the *ortho* position of benzene ring increases. However, for ketones with 2,6-disubstituted aryl substituents the enantiomeric excess increases when catecholborane is used.

1. Introduction

Reduction of a prochiral ketone to an alcohol is a common reaction in organic synthesis. In order to achieve enantioselective reduction of prochiral ketones, various chiral non-racemic reducing reagents have been developed.[1] In an ongoing project in our laboratory we required various chiral non-racemic secondary benzylic alcohols. The obvious choice was to reduce the corresponding aromatic ketones with borane in the presence of oxazaborolidine catalyst[2] due to its wide range of applicability and simplicity of procedure.[1d,e]

2. Results and discussion

When ketones **1**–**3** were subjected to CBS[2a] reduction using B-butyl catalyst **13** and $BH_3 \cdot Me_2S$ as a reducing agent, the enantiomeric excess (*ee*) of the resulting alcohols **7**–**9** decreased as the bulk of the aromatic group increased (Table 1, entries 1–3). This was contrary to our expectations. It has been reported that mesityl methyl ketone can be reduced in high *ee* when catecholborane is used as the reducing agent.[3] In the event, when CBS reduction was carried out using catecholborane as reducing agent there was no noticeable change in the enantiomeric excess of the alcohols formed from

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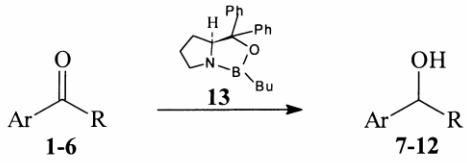
Table 1
Asymmetric reduction of aromatic ketones using oxazaborolidine as catalyst[a]



1-6 7-12

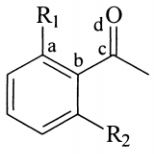
S. No	Ar	R	Ketone	Reducing Agent	Alcohol	ee[b]	Yield (%)
1	Phenyl	CH_3	1	$BH_3.Me_2S$	7	94	90
2	*o*-Toluyl	CH_3	2	$BH_3.Me_2S$	8	89	92
3	Mesityl	CH_3	3	$BH_3.Me_2S$	9	74	88
4	Phenyl	C_2H_5	4	$BH_3.Me_2S$	10	88	93
5	o-Toluyl	C_2H_5	5	$BH_3.Me_2S$	11	81	91
6	Mesityl	C_2H_5	6	$BH_3.Me_2S$	12	65	90
7	Phenyl	CH_3	1	Catechol Borane	7	92	91
8	*o*-Toluyl	CH_3	2	Catechol Borane	8	88	89
9	Mesityl	CH_3	3	Catechol Borane	9	90	87
10	Phenyl	C_2H_5	4	Catechol Borane	10	88	92
11	*o*-Toluyl	C_2H_5	5	Catechol Borane	11	79	90
12	Mesityl	C_2H_5	6	Catechol Borane	12	78	88

[a] In order to avoid any solvent or temperature effect, what so ever it may be, all reactions were carried out in toluene at -10° C. [b] Enantiomeric excess was determined by 300 MHz NMR analysis of corresponding Mosher esters of the alcohols.[7]

acetophenone and methyl *o*-tolyl ketone (Table 1, entries 1, 2 and 7, 8) but there was an appreciable increase in *ee* in the case of mesityl methyl ketone (Table 1, entries 3 and 9). Similar results were also obtained when ketones **4**–**6** were reduced to give alcohols **10**–**12** under the same conditions (Table 1).

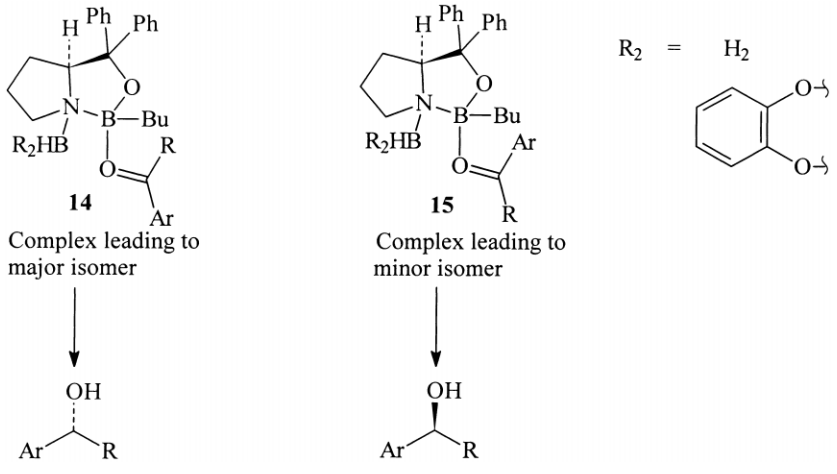
The reduction using CBS catalyst works well when the two groups attached to the carbonyl group to be reduced have significantly different steric bulk.[4] These results clearly indicate that due to the substitution at the *ortho* position the aromatic group takes conformation in such a manner that its effective steric bulk decreases. In order to substantiate this hypothesis, we carried out semi-empirical calculations on ketones **1**–**3**.[5,6] It was found that the dihedral angle abcd for the most stable conformation increases as the substitution on the *ortho* position increases (Table 2). In the case of the mesityl group, it is almost orthogonal to the CO sigma bond. The results obtained in the case of borane reduction can be explained on the basis of these conformations of the different aryl groups. As the substitution increases, the net steric bulk of the aryl group moves away from the carbonyl oxygen lone pair which is *syn* to the aryl group. As a result, the effective steric differentiation of two groups of the ketone decrease and the *ee* also decreases correspondingly. In the case of reduction using catecholborane, the enhancement of the enantiomeric excess for mesityl ketones **3** and **6** can be explained by considering the interaction of one of the *ortho* methyl of mesityl groups with the bulkier catecholborane when it attaches to boron of oxazaborolidine to give a minor isomer via complex **15** (Scheme 1). Due to the small size of borane, this type of interaction

Table 2
Most stable conformation of aromatic ketones as calculated by MM2



Compound	R_1	R_2	Conformer ϕ, deg
1	H	H	30±10
2	CH_3	H	55±5
3	CH_3	CH_3	90±20

will be absent when borane is used as the reducing agent. The molecular models also reveal this fact. On the other hand, phenyl and *o*-tolyl groups can avoid interaction with the catecholborane because they can always place a hydrogen towards catecholborane in complex **15**.



Scheme 1.

In conclusion, we have demonstrated that the conformation of the aryl part of the ketone is important in the outcome of CBS reduction. These results will help in the planning of the synthesis of these types of molecules. These results also add to a small but growing number of examples where the effective steric bulk of the aryl group depends on its conformation in the molecule.[8]

3. Experimental

All the reactions were carried out under a nitrogen atmosphere in flame dried apparatus. Toluene was distilled over sodium/benzophenone. All the ketones were distilled and stored over 4A molecular sieves. (*S*)-(−) α,α-diphenylprolinol was purchased from Aldrich, butyl boronic acid and B-butyl catalyst **13** were prepared using Corey's procedure.[9] All of the alcohols prepared by asymmetric reduction were characterised by comparing their ^{1}H NMR, IR, TLC and mixed TLC with authentic samples.

3.1. General procedure for asymmetric reduction using $BH_3 \cdot Me_2S$ as reducing agent[10]

To a solution of catalyst **13** (0.15 mmol) in 1 ml of toluene, $BH_3 \cdot Me_2S$ (2M solution in toluene, 0.6 mmol) was added at −10°C. Neat ketone (1 mmol) was added slowly at the same temperature over a

period of 15 min. After 30 min the reaction was quenched by adding 2 ml of methanol and the reaction mixture was stirred for an additional 30 min at room temperature. Solvent was removed under reduced pressure and the residue was dissolved in ether. The ether solution was washed with dilute HCl, water, saturated aqueous sodium bicarbonate and finally with brine. The organic layer was dried over anhydrous Na_2SO_4, concentrated under vacuum and purified by flash chromatography using 5% ethyl acetate in hexane as eluent.

3.2. General procedure for asymmetric reduction using catecholborane as reducing agent

To a solution of catalyst **13** (0.15 mmol) in 1 ml of toluene, catecholborane (0.75 ml of 2M in toluene, 1.5 mmol) and ketone (1 mmol) were added at −10°C and the reaction mixture was kept at −10°C for 48 h. The reaction was quenched by adding methanol (2 ml) and solvent was removed under vacuum. The residue was dissolved in ether (10 ml) and the resulting ethereal solution was washed sequentially with saturated aqueous sodium hydroxide, water, dilute HCl and finally with brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified using 5% ethyl acetate in hexane as eluent.

3.3. General procedure for the preparation of Mosher ester[11]

To a mixture of Mosher acid (0.15 mmol), DCC (0.18 mmol) and DMAP (5 mg) in 1 ml of CH_2Cl_2, a solution of alcohol (0.1 mmol) in 0.5 ml of CH_2Cl_2 was added at room temperature. The reaction mixture was stirred overnight at room temperature. Ether (5 ml) was added and the precipitates were removed by filtration. The filtrate was washed sequentially with dilute HCl, water, aqueous sodium bicarbonate and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was passed through a short pad of silica gel to remove baseline material.

Acknowledgements

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