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Asymmetric reduction of acetophenone using α,α-disubstituted aziridinemethanols and borane

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ABSTRACT

A series of α,α-disubstituted aziridinemethanols have been designed and synthesized as chiral auxiliaries for the enantioselective reduction of acetophenone. Some of them catalyzed the reduction with excellent ee (up to 97%) under more facile reaction conditions. Furthermore, the results showed that α,α-disubstituted aziridinemethanols with electron-withdrawing groups led to much higher enantioselectivity than those with electron-donating groups, which allowed the rational modification of catalyst structure to achieve optimal enantioselectivity.

1. Introduction

The enantioselective reduction of prochiral ketones to the corresponding optically active secondary alcohols is an active field of research in enantioselective catalysis [1,2]. One of the most popular methods involves the employment of chiral 1,3,2-oxazaborolidines generated from chiral 1,2-amino alcohols and borane as by Itsuno et al. [3–7] and further developed by Corey et al. [8–12]. This paved the way for the development of oxazaborolidines as chiral catalysts for the borane-mediated enantioselective reduction of a wide variety of prochiral ketones (CBS reduction).

Numerous examples describing the application of this catalyst have been reported [13–23]. Scheme 1 outlines the structure of the chiral 1,3,2-oxazaborolidine **2** formed from proline derived amino alcohol **1** and the general mechanistic model [1,8,24–26] which was developed for reduction of ketones with oxazaborolidine catalyst **2** (and analogous catalysts). Due to the well-defined structure of the catalyst and the straightforward reaction pathway, the scope of the CBS reduction have expanded rapidly and the rational modification of catalyst structure to achieve optimal enantioselectivity for a particular type of substrate have arisen tremendously.

Chiral 1,3,2-oxazaborolidines derived from other 1,2-amino alcohols have also been reported [1]. The reduction of ketones takes place according to the same mechanistic principle as that for oxazaborolidine catalyst **2**. Cyclic amino alcohols derived from azetidines, pyrrolidines, piperidines, etc. have been studied extensively, as basis for 1,3,2-oxazaborolidine catalysts.

Advances in the asymmetric synthesis of catalytic ligands have intensified the search for new, more specific and suitable chiral auxiliaries. Hence, it is still necessary to study chiral small-cyclic heterocycles such as three-membered cyclic amino alcohols. Moreover, it is clearly of great significance for the comparison of the asymmetric reductions with the oxazaborolidine catalysts derived from the corresponding six-, five-, four- and three-membered cyclic amino alcohols. Consequently, in this study, we are particularly interested in oxazaborolidines derived from aziridines (Scheme 2). Zwanenburg et al. have already investigated two classes of aziridine-2-alcohols as precatalyst systems, which could conveniently be converted into the corresponding oxazaborolidines, followed by reducing acetophenone to yield the corresponding alcohol in high optical yields [27]. With the attempt to further widen this type of catalysts, a series of novel α,α-disubstituted aziridinemethanols have been designed and synthesized in order to test their effectiveness in this type of reduction.

2. Experimental

2.1. General

Acetophenone was dried and distilled over calcium hydride. THF was dried and distilled over sodium/benzophenone. Borane-dimethyl sulfide complex and borane-tetrahydrofuran complex were obtained from J&K Chemical Ltd. All the reactions employing

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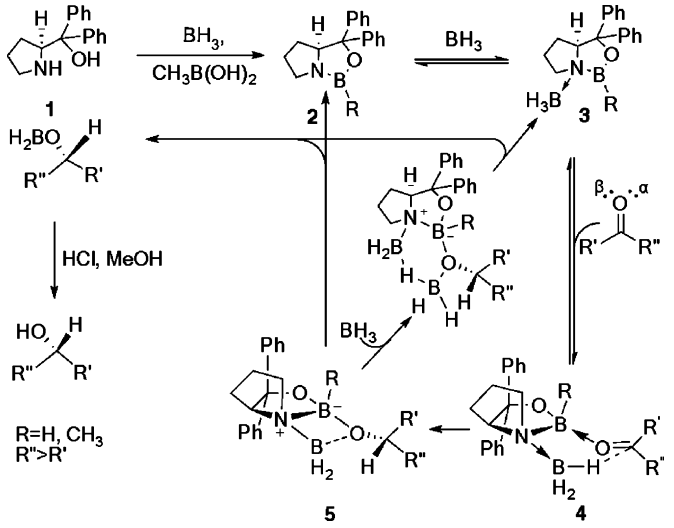
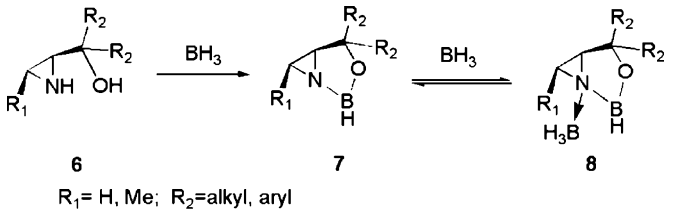


Scheme 1. Proposed mechanism of the oxazaborolidine-catalyzed ketone reduction.

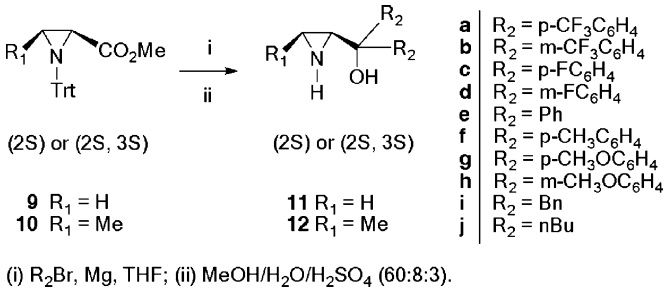
dry solvents were carried out under a positive pressure of argon. Organic extracts were dried over $MgSO_4$ and filtered before removal of the solvent. Melting points were determined on a XT-4 apparatus (uncorrected). IR spectra were obtained at a Perkin-Elmer 983 spectrometer. MS spectra were recorded on a Finnigan-LC Qadvantage spectrometer (ESI), and optical rotations were measured at 20 °C using the Sodium D-line by means of a Perkin-Elmer 343 plus polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 300 or 600 MHz spectrometer. Elemental analyses were carried out on a VarioEL III (German) instrument. Silica gel was used for analytical and flash chromatography. Agilent 1100 (4.6 mm × 250 mm, Diacel Chiracel OD-H column) for HPLC.

2.2. General procedure for the synthesis of 11 and 12

To a stirred suspension of magnesium turnings (2.88 g, 120 mmol, 4.0 equiv.) in THF (100 ml) was gradually added bromide (120 mmol, 48.0 equiv.). After heating the Grignard reagent for 3 h, aziridinecarboxylate **9** (or **10**) (30 mmol) in THF (30 ml) was added dropwise over a period of 20 min. The reaction was monitored by TLC (hexane-EtOAc). After 3 h the reaction was quenched with saturated aqueous NH_4Cl (60 ml). The crude reaction mixture was extracted with ethyl acetate (3× 100 ml) and the combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was dissolved in a mixture of MeOH, water and H_2SO_4 (60:8:3) (150 ml) by sonication for 5 min. After stirring 24 h and subsequent addition of water (100 ml) as ice, the solution was made alkaline with 30% NaOH to pH 10. After the mixture was extracted with ethyl acetate (3× 100 ml), the organic phase was washed with sat. $NaHCO_3$ (3× 50 ml) sat. NaCl (3× 50 ml), dried over $MgSO_4$ and



Scheme 2. Oxazaborolidine BH_3 complex formation from α,α-disubstituted aziridinemethanol.



Scheme 3. Synthesis of α,α-disubstituted aziridinemethanols.

concentrated in vacuo. The products were purified by flash column chromatography to yield **11** (or **12**) (Scheme 3).

2.3. General procedure for asymmetric reduction of acetophenone

Under an argon atmosphere, $BH_3{\cdot}SMe_2$ (0.6 mmol) was added to a solution of aziridinemethanol catalyst **11** (or **12**) (0.2 mmol) in THF (8 ml). The solution was stirred and refluxed for 1 h. After the addition of $BH_3{\cdot}SMe_2$ (1.2 mmol), then a THF (2 ml) solution of acetophenone (2.0 mmol) was added immediately. After the addition was completed, the reaction was quenched with methanol (1 ml) and 5% H_2SO_4 (5 ml) was added with stirring. The mixture was extracted with diethyl ether (2× 5.0 ml). The organic layer was treated with saturated $NaHCO_3$ solution and brine, and then dried over anhydrous Mg_2SO_4. After removal of solvent, the residue was purified by flash column chromatography on silica gel to give the product: (R)-(+)-1-phenyl-1-ethanol. The ee value was determined by Chiralcel OD-H column, t_R = 11.7; t_S = 13.9 (hexane/iPrOH 90:10, flow 0.5 ml/min) [28].

3. Results and discussion

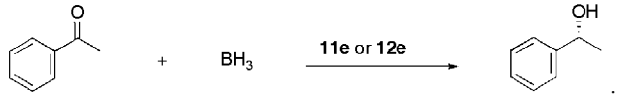
3.1. Aziridinemethanol catalysts preparation

The general procedure for preparation of α,α-disubstituted aziridinemethanols is illustrated in Scheme 3. Methyl *N*-tritylaziridine-2-carboxylates **9** and **10** were synthesized from L-serine and L-threonine [29], and then allowed to react with a Grignard reagent in THF at ambient temperature. The trityl group was removed *in situ* with H_2SO_4 in mixed MeOH/H_2O solution [30,31] to provide aziridinemethanols **11** and **12** in reasonable yields.

3.2. Establishment of catalysis conditions and method

It is well known that the stereoselectivity of reduction is affected greatly by solvent, temperature and the amount of catalyst. To find the optimum reaction conditions, we examined the reduction of acetophenone with **11e** and **12e** under various experimental conditions. The detailed results are outlined in Table 1. First, solvent effects were examined. To aziridinemethanol catalyst **11e**, at room temperature, the reductions were completed within 5 h in toluene and 3 h in THF with low ee values (entries 1 and 2). When the reaction temperature was raised from room temperature to reflux in THF, the reduction was complete in 5 min and the ee value increased from 42% to 81% (entries 1 and 4). Apart from the reaction temperature and solvent, the ratio of the catalysts has an impact on the reduction. When the amount of catalyst was increased from 5 to 10 mol.%, the enantiomeric excess increased from 65% to 91% (entries 5 and 6). The method of reduction also affected the results (entries 4 and 5). It is clear that all things considered THF at reflux provide the best results [21,27]. As to aziridinemethanol **12e**, the

Table 1
Effect of temperature, solvent, the amount of catalyst and method.[a]



Entry	Solvent	Catalyst (%)	Method	Temperature	Yield[g]	ee (%)[h]
1	THF	11e 10 mol.%	[b]	rt	65	42
2	Toluene	11e 10 mol.%	[b]	rt	71	30
3	Toluene	11e 10 mol.%	[c]	Reflux	81	23
4	THF	11e 10 mol.%	[b]	Reflux	94	81
5	THF	11e 10 mol.%	[d]	Reflux	97	91
6	THF	11e 5 mol.%	[d]	Reflux	90	65
7	Toluene	12e 10 mol.%	[c]	Reflux	78	29
8	THF	12e 10 mol.%	[c]	Reflux	95	48
9	THF	12e 10 mol.%	[b]	rt	80	18
10	THF	12e 10 mol.%	[d]	Reflux	97	63
11	THF	12e 10 mol.%	[e]	Reflux	96	25
12	Toluene	12e 5 mol.%	[f]	rt	49	25

[a] Experiments were performed on a 2.0 mmol scale.
[b] $BH_3{\cdot}SMe_2$ (2.2 mmol) was added to a solution of aziridinemethanol catalyst (0.20 mmol) in THF (8 ml). The solution was stirred for 1 h. Then a THF (2 ml) solution of ketone (2.0 mmol) was added dropwise within 30 min.
[c] $BH_3{\cdot}SMe_2$ (2.2 mmol) was added to a solution of aziridinemethanol catalyst (0.20 mmol) in THF (8 ml). The solution was stirred for 1 h. Then a THF (2 ml) solution of ketone (2.0 mmol) was added immediately.
[d] $BH_3{\cdot}SMe_2$ (0.6 mmol) was added to a solution of aziridinemethanol catalyst (0.20 mmol) in THF (8 ml). The solution was stirred for 1 h. After the addition of $BH_3{\cdot}SMe_2$ (1.2 mmol), a THF (2 ml) solution of ketone (2.0 mmol) was added immediately.
[e] $BH_3{\cdot}$THF (0.6 mmol) was added to a solution of aziridinemethanol catalyst (0.20 mmol) in THF (8 ml). The solution was stirred for 1 h. After the addition of $BH_3{\cdot}SMe_2$ (1.2 mmol), a THF (2 ml) solution of ketone (2.0 mmol) was added immediately.
[f] To a solution of catalyst $BH_3{\cdot}$THF (0.25 mmol) was added, stirring for 10 min, after the addition of acetophenone, a $BH_3{\cdot}SMe_2$ solution in toluene (2.5 mmol) was added immediately.
[g] Yields of isolated products after purification by column chromatography.
[h] Determined by using chiral HPLC.

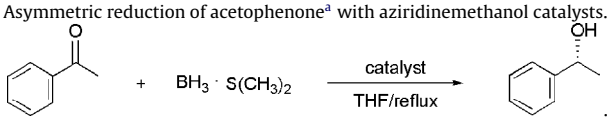
similar result was achieved. In addition, $BH_3{\cdot}SMe_2$ is the better reagent formed chiral 1,3,2-oxazaborolidine than $BH_3{\cdot}$THF (entries 10, 11 and 12).

3.3. Asymmetric reduction of acetophenone using various aziridinemethanol catalysts

Having established the best reaction conditions and method, the application of various α,α-disubstituted aziridinemethanols to the reduction of acetophenone was investigated using a catalytic amount (10 mol.%) of aziridinemethanol catalysts in refluxing THF. The results were summarized in Table 2. Except entries 9, 10, 19, 20 with relatively slow rate, the other reductions completed in 5 min. Excellent yields were obtained in these reductions and excellent enantiomeric excesses were obtained for entries 1–5, 11 and 12.

It can be concluded that the disubstitution groups on the hydroxy-bearing carbon play crucial role in the enantiomeric purity of the reduction of acetophenone. Firstly, aryl groups disubstituted on hydroxy-bearing carbon appear to favor the enantioselectivity than those with benzyl and alkyl groups. Secondly, the results also demonstrate that the electronic effects have a significant impact on the enantioselectivity. Comparison of the results of catalysts **11a**–**j** (or **12a**–**j**) indicates that electron-withdrawing groups are much beneficial for enantioselectivity than electron-donating groups. According to the general mechanistic model (Scheme 1), it can be deduced that for amino alcohols **11** (or **12**) electron-withdrawing groups disubstituted on hydroxy-bearing carbon contribute to produce the chiral 1,3,2-oxazaborolidine **2** and also to increase the Lewis acidity of the endocyclic boron atom. The strongly Lewis

Table 2
Asymmetric reduction of acetophenone[a] with aziridinemethanol catalysts.



Entry	Catalyst	Yield (%)[b]	ee (%)[c]	Absolute config.[d]
1	11a	96	97	R
2	11b	94	93	R
3	11c	97	95	R
4	11d	95	90	R
5	11e	95	91	R
6	11f	93	74	R
7	11g	94	42	R
8	11h	92	54	R
9	11i	94	23	R
10	11j	95	26	R
11	12a	95	92	R
12	12b	96	94	R
13	12c	94	88	R
14	12d	95	84	R
15	12e	93	63	R
16	12f	95	57	R
17	12g	94	55	R
18	12h	94	53	R
19	12i	93	37	R
20	12j	95	56	R

[a] Experiments were performed on a 2.0 mmol scale.
[b] Yields of isolated products after purification by column chromatography.
[c] Determined by using chiral HPLC.
[d] The absolute configurations were determined by optical rotation.

acidic complex then binds to the ketonic substrate more readily, at the more sterically accessible electron lone pair and *cis* to the vicinal BH_3 group, face-selective hydride transfer via a six-membered transition state takes place to form the reduction product **5**, resulting in enhanced reaction rate and enantioselectivity. For the electron-donating groups, just the reverse is true. For amino alcohols **12** (**a**–**j**), although lower ee value was obtained by catalyst **12e** compared with previous data [27], it is still effective and reasonable to differentiate the asymmetric induction capability of substitutions on hydroxy-bearing carbon of aziridinemethanols under the current conditions. Favorable ees can be gained for **12a**–**d**.

In addition, possibly the methyl group on the C-3 position of aziridine affects the reduction process negatively with regard to ee by steric hindrance effect, which leads entries 13–15 with lower ee values compared with entries 3–5. The combination of C-2 and C-3 configurations in aziridine moiety also has influences on the stereoselectivity of reduction.

4. Conclusion

The present study offers a practical, effective and highly enantioselective manner for the catalytic reduction of acetophenone by using α,α-disubstituted aziridinemethanols under facile reaction conditions, wherein an efficient type of oxazaborolidine catalysts basing on three-membered cyclic amino alcohols has been extended. It is proved that the electronic effects of the substituent groups on the hydroxyl-bearing carbon of aziridinemethanols have important impacts on the enantioselectivity of the reduction of acetophenone. Electron-withdrawing groups substituted on the hydroxyl-bearing carbon can promote the enantioselectivity of the reduction, which allows the rational modification of catalyst structure to achieve optimal enantioselectivity.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molcata.2008.10.031.

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