Available online at www.sciencedirect.com
SCIENCE DIRECT
Journal of Molecular Catalysis A: Chemical 244 (2006) 68–72
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
www.elsevier.com/locate/molcata

(*S*)-2-Aryl-4,4-diphenyl-3,1,2-oxazaboro[3.3.0]octanes: Efficient catalysts for the asymmetric borane reduction of electron-deficient ketones

Han Liu, J.X. Xu *

Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, PR China

Received 27 July 2005; received in revised form 31 August 2005; accepted 31 August 2005
Available online 6 October 2005

Abstract

The obvious influence of electronic effects of ketones on the enantioselectivities was observed previously in the oxazaborolidine-catalyzed asymmetric borane reduction of ketones. On the basis of the catalytic reduction mechanism, the electronic effect of organocatalysts, B-aryl-substituted oxazaborolidines, was tuned rationally to improve the enantioselectivities of the electron-deficient ketones in the reduction. The results indicate that all B-aryloxazaborolidines show excellent enantioselectivities for the electron-deficient ketones. This indicates that B-aryloxazaborolidines show better enantioselectivities than B-unsubstituted and B-methoxy-substituted oxazaborolidines for the electron-deficient ketones.

Keywords: Asymmetric reduction; Borane; Electronic effect; Enantioselectivity; Ketone

1. Introduction

Chiral 1,3,2-oxazaborolidine-catalyzed borane reduction of prochiral ketones to chiral secondary alcohols is one of the most important reactions in asymmetric syntheses, which has been widely used during the past decade [1]. Numerous new efficient oxazaborolidine catalysts have been reported and a plethora of applications have appeared till now. In comparison with the numerous attempts to search for new catalysts to improve the enantioselectivity, several papers have concentrated on the mechanistic investigation of the catalytic asymmetric reduction [2,3]. Some papers have been paid attention to the factors which affect the enantioselectivity in the asymmetric reduction, such as the structure [1,2,4], the stability [2a,5] (including dimerization) and the loading amount [2a,5a,6] of the catalyst, the borane source [7] and amount [2a,6c], the order and rate of the addition of a ketone or borane into a reductive system [1d,6c], the reduction temperature [5d,6c,8], the solvent [5a,6c,7c], the additive [8g,9,10], the secondary reduction [9a,11], the stabilizer in borane [12], the electronic effects of ketones [4a,5a,10,13], etc. Although a few papers have considered on the influence of the electronic effects of catalysts on the enantioselectivity, most of the results indicated that no obvious influence has been observed in the asymmetric reduction [4a,5a]. Very recently we investigated the influence of the electronic effects of ketones on the enantioselectivity in the asymmetric reduction and found that the electron-deficient ketones generally give lower enantioselectivities [10].

The factors governing enantioselectivity in the catalytic asymmetric reaction are usually interpreted in steric terms [14] affected by the temperature and solvent, etc. [5a,6c,7c,8]. Electronic effects have become an important factor to control the enantioselectivity in recent investigations [15]. It should be very useful to understand all factors, which affect the enantioselectivity, and it will be helpful to apply the asymmetric reaction effectively to a variety of substrates. Herein, we wish to present our investigation on the influence of the electronic effects of catalysts on the enantioselectivity in the asymmetric borane reduction of the electron-deficient ketones.

2. Experimental

2.1. General methods

^{1}H spectra were recorded on a Varian Mercury 200 (200 MHz) and Mercury Plus 300 (300 MHz) spectrometer in

* Corresponding author. Tel.: +86 10 6275 1497; fax: +86 10 6275 1708.
E-mail address: jxxu@pku.edu.cn (J.X. Xu).

1381-1169/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.molcata.2005.08.055

$CDCl_3$ solution with TMS as an internal standard and chemical shifts are reported in ppm. Optical rotations were measured on a Perkin-Elmer Model 341LC polarimeter with a thermally jacketed 10 cm cell (concentration *c* given as g/100 mL). HPLC analyses were performed on an HP1100 HPLC equipment. The e.e. values were determined by HPLC analysis with chiralcel AD, AS, OB, OD, or OD-H columns (4.6 mm × 250 mm) with a mixture of *n*-hexane–isopropanol as an eluent. Borane–dimethyl sulfide complex and substituted arylboric acids were purchased from Acros Chemicals Co. Toluene was heated under reflux over sodium and distilled prior to use.

2.2. General procedure for the preparation of catalysts *1d–g*

A 25 mL round-bottomed flask equipped with a stirring bar and a 10 mL pressure-equalizing addition funnel (containing a cotton plug and ca. 10 g of 5 Å molecular sieves, and functioning as a Soxhlet extractor) [16]. A mixture of (*S*)-diphenylprolinol (0.05 mmol, 12.7 mg) and arylboronic acid (0.05 mmol) was solved in 15 mL of dry toluene. The resulting solution was heated to reflux for 12 h. Then most of the solvent was distilled off and the residue (ca. 3 mL) was cooled to room temperature. The addition funnel was removed off and the flask was airproofed quickly to avoid moisture. The catalyst can be used directly without further purification.

2.3. General procedure for the asymmetric reduction of ketones using catalysts *1d–g*

To a solution of the catalyst (0.05 mmol, 10 mol%) that was freshly prepared in dry toluene, 2 mol/L borane–dimethyl sulfide complex in THF (0.25 mL, 0.5 mmol) was added under a nitrogen atmosphere at room temperature. Then the solution was warmed or cooled to the desired temperature and stirred for 15 min. A solution of ketone (0.5 mmol) in 4 mL of toluene was then added dropwise over 1 h. After the addition, the resulting solution was stirred for 4 h and then quenched with 0.5 mL of methanol in an ice bath. After concentration under reduced pressure, the residue was purified on a silica gel column with a mixture of petroleum ether (60–90 °C) and ethyl acetate (5:1, v/v) as an eluent to give chiral secondary alcohol as a colorless oil. The spectral and analytical data of all obtained alcohols are in agreement with those reported in the literature [10,17,18]. The e.e. value was determined by chiral HPLC analysis.

2.4. (*R*)-1-(4-Bromo-3-nitrophenyl)ethanol (*3c*)

Colorless liquid; $[\alpha]_D^{20}$ = +25.0 (c, 0.5, CH_2Cl_2), e.e. 98%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.50 (d, J = 6.4 Hz, 3H, CH_3), 1.88 (s, br, 1H, OH), 4.95 (q, J = 6.4 Hz, 1H, CH), 7.43 (d, J = 8.4 Hz, 1H, ArH), 7.69 (d, J = 8.4 Hz, 1H, ArH), 7.86 (s, 1H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 25.38, 68.79, 112.74, 122.53, 130.13, 135.00, 146.57, 147.01. MS (EI) *m/z*: 245 (M^+), 247, 230, 232, 185, 187, 155, 157, 102, 75, 51; IR ν (cm^{-1}): 3350 (OH), 2975, 2925, 1534, 1355. Racemate was reported in the literature [17].

2.5. (*R*)-1-(3,5-dinitrophenyl)ethanol (*3d*)

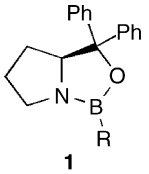
Colorless solid; $[\alpha]_D^{20}$ = +25.9 (c, 1.0, $CHCl_3$), e.e. 98%; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.61 (d, J = 6.4 Hz, 3H, CH_3), 2.09 (s, br, 1H, OH), 5.16 (q, J = 6.4 Hz, 1H, CH), 8.60 (s, 2H, ArH), 8.95 (s, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 25.67, 68.69, 116.01, 117.65, 125.75, 148.61; MS (EI) *m/z*: 211 ($M^+ - 1$), 197, 166, 152, 105, 91, 75, 51; IR ν (cm^{-1}): 3353 (OH), 2916, 1541, 1345, 731. Racemate was reported in the literature [18].

3. Results and discussion

It has been proven that chiral (*S*)-2-substituted 4,4-diphenyl-3,1,2-oxazaboro[3.3.0]octanes **1**, derived from (*S*)-2-(diphenylhydroxymethyl)pyrrolidine, with several different substituents (such as R is H for **1a**, Me for **1b**, MeO for **1c** and Ph for **1d**, as representatives, 4-FPh for **1e**, 4-ClPh for **1f**, 3-NO_2Ph for **1g**, Scheme 1) on B atom are the most effective catalysts in the asymmetric reduction with excellent yields and enantioselectivities for a wide variety of ketones [1,2,6]. We have found that catalyst **1c** is an effective, convenient and practical catalyst because it can be prepared from (*S*)-2-(diphenylhydroxymethyl)pyrrolidine and inexpensive trimethyl borate in situ and used directly without any further separation and purification [6]. However, after the investigation on the influence of the electronic effects of ketones on the enantioselectivity [10] it seems that catalyst **1c** is not efficient to the ketones with electron-withdrawing groups. The results prompt us to consider tuning the influence of the electronic effects of the catalysts rationally to improve the enantioselectivity of the reduction of the ketones with electron-withdrawing groups on the basis of the reaction mechanism of the asymmetric reaction.

On the basis of our previous investigation and analysis [10] the coordination step in the catalytic cycle is a key step for the enantioselectivity, in other words, an e.e.-determining step in the reduction cycle. The efficient coordination between a catalyst and a ketone will afford the excellent enantioselectivity. To improve the enantioselectivity of the electron-deficient ketones, which have a relative hard oxygen atom (hard base), according to the Pearson's hard–soft acid–base rule, we need to use a catalyst with a relative hard boron atom (hard acid), e.g. the catalyst has an electron-withdrawing group on its boron atom (Scheme 2).

We hope to tune the electronic effects of the catalysts by using (*S*)-2-aryl-4,4-diphenyl-3,1,2-oxazaboro[3.3.0]octanes **1d–g**



1

a: R = H, **b:** R = Me, **c:** R = MeO, **d:** R = Ph,
e: R = 4-FPh, **f:** R = 4-ClPh, **g:** R = 3-NO_2Ph

Scheme 1. (*S*)-2-Substituted 4,4-diphenyl-3,1,2-oxazaboro[3.3.0]octane catalysts.