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Journal of Molecular Catalysis A: Chemical 284 (2008) 40–45
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
www.elsevier.com/locate/molcata

Unexpected influence and its origin in rationally tuning the electronic effect of catalysts in the asymmetric borane reduction of ketones

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Received 15 May 2007; received in revised form 9 January 2008; accepted 10 January 2008
Available online 18 January 2008

Abstract

Rationally tuning the electronic effect of catalysts is one of the most important strategies to improve stereoselectivity in asymmetric catalysis. (*S*)-2-aryl-3,1,2-oxazaborobicyclo[3.3.0]octanes, which can be considered as electronically tuned (*S*)-2-phenyl-3,1,2-oxazaborobicyclo[3.3.0]octane, were prepared and evaluated in the asymmetric borane reduction of ketones. An unexpected influence of the electronic effect of catalysts on the enantioselectivity was observed and attributed to the catalyst dimerization that was further confirmed experimentally. The unsuccessful tuning is accounted for by assuming that hydride transfer in the catalytic cycle is the rate-determining step in the reduction catalyzed by *B*-aryl catalysts.

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

1. Introduction

Factors governing the enantioselectivity of asymmetric catalysis have always been one of the crucial concentrations in organic chemistry. The asymmetric induction with enantiopure catalysts has been recognized to depend mainly on steric repulsion between the catalyst backbones (including substituents) and substrates [1]. However, more and more examples have been observed of the enantioselectivity being also dependent on the electronic effect of substrates, even with very similar structural features, for the same catalysts in asymmetric catalysis [2]. To understand and to solve this problem, alternatively, a strategy of "the electronic control" or "the electronic tuning" via variation of the electronic character of catalysts to optimize the stereoselectivity has been attempted and investigated in the last two decades [3]. Although prominent electronic-character-dependence of catalysts on the stereoselectivity was observed in some cases [4,5], the underlying reasons still remain obscure in most cases [6].

The catalytic enantioselective borane reduction of ketones catalyzed by the enantiopure oxazaborolidines shows not only a very broad range of practical applications [7], but also the insights into mechanistic details [8] and numerous factors affecting the enantioselectivity, such as the dimerization of catalysts [8a,9], the temperature [9b,10], the solvent [8a,9a,10], the borane source[11], and the electronic effects of ketones [12] and catalysts [13]. This would facilitate our investigation into the rational tuning of the electronic effect of catalysts in the asymmetric catalysis. Previously, almost all of examples on the electronic tuning of catalysts focused on the chiral ligand–metal complex-catalyzed asymmetric catalyses [3–5]. To the best of our knowledge, only a few examples on the electronic tuning of organocatalysts have been reported [5a,b,12b,13]. Although a few papers have considered the influence of the electronic effect of catalysts on the enantioselectivity in the asymmetric borane reduction of ketones, it is indicated that no obvious influence has been observed because most of the reported catalysts show very high enantioselectivities. All enantioselectivities are more than 95% e.e. so that no enough observation scope remains [5a,13]. Herein, we wish to present our results on the rational electronic

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1381-1169/$ – see front matter © 2008 Published by Elsevier B.V.
doi:10.1016/j.molcata.2008.01.018

tuning of catalysts in the oxazaborolidine-catalyzed asymmetric borane reduction of ketones.

2. Experimental

2.1. General methods

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury Plus 300 (300 MHz) spectrometer in $CDCl_3$ solution with TMS as an internal standard and ^{19}F NMR spectra were obtained on the same spectrometer in toluene solution with CF_3CO_2H as an external standard. HPLC analyses were performed on an HP1100 HPLC equipment. Arylboronic acids and borane-dimethyl sulfide complex were purchased from Acros Chemicals Co. Toluene and THF were heated under reflux over sodium benzophenone ketyl and distilled prior to use.

2.2. General procedure for the asymmetric reduction of ketones with catalysts 2

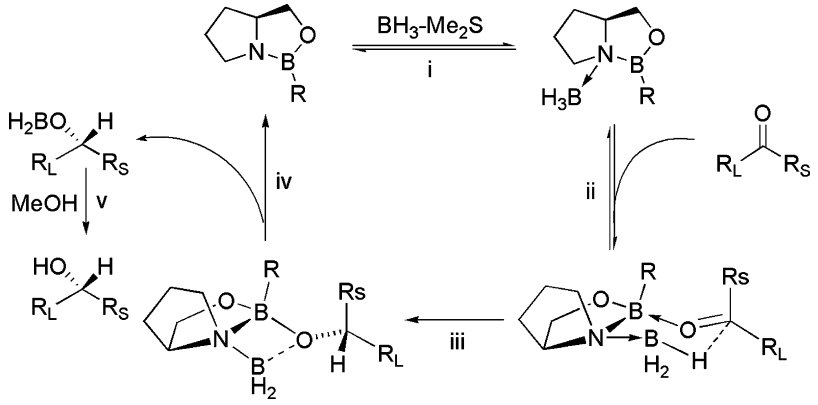
A 25 mL round-bottomed flask equipped with a stirring bar and a 10 mL pressure-equalizing addition funnel (containing a cotton plug and ca. 10 g of 5 A molecular sieves, and functioning as a Soxhlet extractor). A mixture of (*S*)-prolinol (0.05 mmol, 5.1 mg) and arylboronic acid (0.05 mmol) was dissolved in dry toluene (15 mL). The resulting solution was heated to reflux for 12 h. After most of the solvent was distilled off, the residue (ca. 3 mL) was cooled to room temperature (all solvent was removed for reductions in THF and dry THF (3 mL) was added). The addition funnel was removed and the flask was airproofed quickly to avoid moisture. The catalyst **2** was used directly without further purification.

To a solution of the freshly prepared catalyst **2** (0.05 mmol, 10 mol%) was added 2 mol/L borane-dimethyl sulfide complex in THF (0.25 mL, 0.5 mmol) under a nitrogen atmosphere at room temperature. The resulting solution was tuned to the desired temperature and stirred for 15 min. A solution of ketone **6** (0.5 mmol) in 4 mL of the desired solvent was then added dropwise over 1 h. After the addition, the resulting solution was stirred for 4 h and 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 e.e. values were determined by chiral HPLC analysis.

3. Results and discussion

It is generally accepted that the asymmetric borane reduction involves four key steps (Scheme 1) [8]: (1) coordination of borane to a catalyst, (2) complexation of a ketone to the endocyclic boron in the catalyst via the Lewis acid–base interaction, (3) hydride transfer to the carbonyl carbon of the ketone and (4) dissociation of an alkoxyborane moiety and regeneration of the catalyst. Some experimental and calculational results indicate that the rate-limiting step might be either the ketone–catalyst complexation or the hydride transfer step in the catalytic cycle [8c,12b,14]. In either case, especially for the first case, electron-deficient oxazaborolidines were assumed to accelerate the rate-limiting step. Moreover, we found that the non-catalytic reduction should take main responsibility for the generation of the racemic products [10]. Thus, we presumed that electron-deficient catalysts would show higher enantioselectivity than electron-rich ones, especially for electron-deficient ketones, because electron-deficient catalysts would favor the complexation with a ketone. It was partly proved in our previous experimental results although the enantioselectivity was not markedly different (10% e.e. was improved from catalysts **1a** to **1e** for 4-nitroacetophenone) [12b].

According to our previous results, electron-deficient substituted ketones show lower enantioselectivity than electron-rich ones under the catalysis of catalysts **3** and **4** (Scheme 2) [12b]. Recently we started a project on tuning the electronic effect of catalysts rationally to improve the enantioselectivity in the asymmetric catalysis. To tune the electronic effect of catalysts effectively, we used the *B*-aryl catalysts **1**, which can be considered as the electronically tuned *B*-phenyl catalyst **1c**. Although in previous explanation [5a,13], no obvious influence of the electronic effect of catalysts on the enantioselectivity was observed, we thought that only little extent of the e.e. value variation will remain because very high enantioselectivities were obtained with catalysts **1**.



Scheme 1. General accepted mechanism for the oxazoborolidine-catalyzed asymmetric reduction of ketones.