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Synthesis of a class of new phosphine-oxazoline ligands and their applications in palladium-catalyzed asymmetric addition of arylboronic acids to isatins

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ABSTRACT

A class of new phosphine-oxazoline ligands was prepared from commercially available and inexpensive starting materials. As the first example, in situ formed catalysts generated from chiral phosphine-oxazolines and $Pd(OAc)_2$ were successfully applied to the asymmetric addition reactions of arylboronic acids to isatins, and 3-aryl-3-hydroxyoxindoles were obtained in up to 97% yields and good enantioselectivities (up to 88% ee). Up to 98% enantiopurity of the products were obtained after one recrystallization.

1. Introduction

Oxazoline moieties are ubiquitous and privileged structural elements of chiral ligands [1]. Chiral oxazolines are one of the most successful and versatile ligands in asymmetric catalysis [2]. Since the first phosphine-oxazoline ligands (PHOX) were synthesized by Pflatz, Helmchen and Williams in 1993 [3–5], derivatives of these ligands have been continuously developed by introducing different chiral elements into the ligand backbones [2,6]. Many novel chiral phosphino–oxazoline ligands such as PHOX derivatives [2,7–14], spiro backbone phosphino–oxazoline [15,16], chiral axis-fixed biaryl phosphine-oxazoline ligands [17–25], ferrocenylphosphine-oxazoline (Fc-PHOX) [26] and StePHOX [27] were successfully prepared and applied in metal-catalyzed asymmetric reactions.

Chiral 3-substituted 3-hydroxyoxindoles structural cores with a quaternary carbon center at the 3-position are encountered in a large variety of natural products with a wide spectrum of biological and pharmacological activities [28,29], such as dioxibrassinines [30], TMC-95A [31], donaxaridine [32] and convolutamydine A [33]. Studies on the structure–activity relationship showed that configuration of the quaternary carbon stereocenter and substituent of the oxindole has profound influence on the biological and pharmacological activities of those compounds [34]. Catalytic asymmetric addition of nucleophiles to isatins is the most straightforward and powerful approach to this structural scaffold. Some successful asymmetric reactions have been developed in recent years [35–38]. In 2006, Hayashi et al. reported the first catalytic asymmetric addition of arylboronic acids to isatins by using Rh/(R)–MeO–MOP complex as the catalyst [35], and the adducts were produced in high enantioselectivities and excellent yields. Minnaard and co-workers employed a phosphoramidite–rhodium catalyst to this reaction and obtained 3-phenyl-3-hydroxyoxindole in 99% yield and 55% ee [36]. Since rhodium is expensive and rare, replacement of rhodium with cheaper metal such as palladium for this reaction is warmly expected and promising from academic viewpoint and practical application. However, up to now only limited results were reported by employing biphenyl phosphinoimine [39] or N-heterocyclic carbene [40] as the ligand for palladium-catalyzed asymmetric arylation of isatins. Development of more effective ligands and suitable catalytict systems for this

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reaction remains significant and challenging [41]. Axially chiral biaryl phosphine-oxazoline has a structure similar to the biphenyl phosphinoimine and *N*-heterocyclic carbene ligands [39,40]. Moreover, it owns an easily adjustable modular oxazoline moiety. On the basis of the effectiveness for the latter ligands in the reaction, we selected phosphine-oxazoline–palladium catalytic system as our study. Herein, we disclose the synthesis of H_8-BINOL-derived phosphine-oxazoline ligands and their applications in palladium-catalyzed asymmetric addition of arylboronic acids to isatins. The addition reactions acquired good yields and enantioselectivities under mild conditions.

2. Experimental

2.1. General considerations

Anhydrous solvents were dried and distilled according to standard laboratory methods under an atmosphere of nitrogen prior to use. Aryl boronic acids were purchased commercially or prepared according to the literatures and purified by passing through a silica gel column before used. If not mentioned, all other reagents were purchased from commercial sources and used without further purification. All moisture sensitive reactions were carried out under an inert atmosphere of dry nitrogen and were monitored by TLC. ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectra were recorded on a Varian Mercury-Plus 300 spectrometer at 300, 75 and 121.4 MHz, respectively. Chemical shifts (δ) are given in ppm and are referenced to residual solvent peaks (^{1}H NMR and ^{13}C NMR) or to an external standard (85% H_3PO_4, ^{31}P NMR). HR-MS was carried out on a Bruker APEX 47e ESI FT-ICR mass spectrometer and Thermo MAT95XP EI-FAB-CI mass spectrometer. Optical rotations were recorded on a Perkin-Elmer Model 341 polarimeter. HPLC analysis was performed on an Agilent 1200 series system.

2.2. General procedure for the catalytic asymmetric addition of arylboronic acids to isatins

A solution of Pd $(OAc)_2$ (2.25 mg, 0.01 mmol) and (S_a,*S*)-**8g** (9.78 mg, 0.012 mmol) in THF (1.0 mL) was stirred for 30 min at room temperature. KOH (11.2 mg, 0.2 mmol), isatins (0.20 mmol), arylboronic acids (0.4 mmol) and additives (0.03 mmol) were added successively with additional THF (1.0 mL). The resulting mixture was stirred for 48 h at room temperature. Then the solvent was removed under vacuum and the residue was purified by flash column chromatography using silica gel with ethyl acetate/petroleum ether as eluent.

3. Results and discussion

3.1. Synthesis of ligands *8*

The concise synthetic route to the phosphino-oxazoline ligands **8** was shown in Scheme 1. Most of the reactions proceeded in excellent yields, and the final products were obtained readily from (*S*)-(−)-1,1′-bi(2-naphthol) in eight steps. Catalytic hydrogenation of (*S*)-BINOL (Pd/C, EtOH) and subsequent recrystallization from n-heptane provided (*S*)-H_8-BINOL in >99% ee [42]. This compound was then treated with triflic anhydride (CH_2Cl_2, pyridine, 0 °C) to form **2** in 91% isolated yield [43]. Bis(triflate) **2** was exposed to carbon monoxide (1 atm) and an excess of methanol in the presence of palladium acetate (15 mol%) and 1,3-bis(diphenylphosphino)propane (dppp; 15 mol%) to give monocarbonylation product **3** in 63% yield [43]. The aryl phosphine oxide moiety was introduced by reacting **3** with $Ar_2P(O)H$ in DMSO at 120 °C in palladium acetate (10 mol%), 1,4-bis-(diphenylphosphino)butane (10 mol%) and *i*-Pr_2NEt to afford **4** in 81–89% yields [43]. Hydrolysis of carboxylates **4** with aqueous KOH in methanol provided acids **5** in 93–99% yields after recrystallization from hot chloroform. Condensation of **5** with different enantiomerically pure 2-amino alcohols in the presence of 1-hydroxylbenzotriazole (HOBt) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDCI) in DMF [44] gave amides **6** in 92–95% yields. The amides were subjected to oxazoline ring formation by treatment with triethylamine and methanesulfonyl chloride in the presence of a catalytic amount of 4-dimethylaminopyridine in dichloromethane [45,46]. Finally, target ligands **8** were obtained in 73–85% yields via a standard silane reduction using trichlorosilane and *N*,*N*-diisopropylethylamine in refluxing toluene. The molecular structure of **8c** was confirmed by single-crystal X-ray diffraction (Fig. 1) [47]. It is worthy to note that the ligands **8** are stable enough and can be purified by silica gel column chromatography. This characteristic is especially important for scale-up of the reactions.

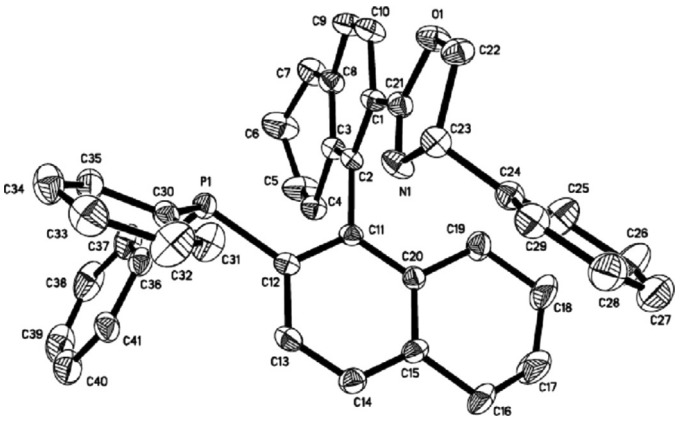

Fig. 1. X-ray crystal structure of ligand **8c** (ORTEP drawing).

3.2. Catalytic asymmetric addition of arylboronic acids to isatins

With ligands **8** prepared, we first examined their enantioselectivities for the palladium-catalyzed phenylboronic acid addition to benzyl-protected isatin along with some other ligands available in our laboratory. The results were summarized in Table 1. The reactions were performed by employing $Pd(OAc)_2$ as palladium source, 2-naphthol and $LiOH{\cdot}H_2O$ as additives. Interestingly, using (S_a,*S*)-**8a** as the ligand, the reaction afforded the arylated product in 71% yield and 54% ee (Table 1, entry 1). Although higher catalytic activity was observed for (S_a,*S*)-**8b** with an electron-rich cyclohexyl substituent, the enantioselectivity dropped sharply (Table 1, entry 2). Compared with the oxazoline ring bearing an *i*-Pr group, ligand (S_a,*S*)-**8c** with a phenyl group provided better enantioselectivity of 66% ee (Table 1, entry 3 vs entry 1). The poor results for ligand (S_a,*R*)-**8d** revealed the importance of chirality match of the oxazoline ring with the axially chiral biphenyl backbone (Table 1, entry 3 vs entry 4). Based on our initial screening results (Table 1, entries 1–4), we turned to examine the performances of ligands (S_a,*S*)-**8e**–**8g** with various aryl groups linked to the P atoms, and ligand (S_a,*S*)-**8g** with 3,5-di-tert-butyl phenyl groups furnished the highest activity and enantioselectivity for the Pd-catalyzed arylation of isatin (Table 1, entry 7). Ligand (S_a,*S*)-**8e** and **8f** with less bulky 4-methylphenyl and 3,5-di-methylphenyl groups, exhibited slightly lower activities and enantioselectivities (Table 1, entries 5–7). Further fine-tuning the substituents R on the oxazoline ring ligands (S_a,*S*)-**8h**–**8j** did not gave better results (Table 1, entries 8–10), and (S_a,*S*)-**8g** was the most effective ligand for the arylation reaction.