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Enantioselective Hydrogenation of α-Dehydroamino Acid Esters Catalyzed by Rhodium Complexes with Chiral Bisaminophosphine Ligands

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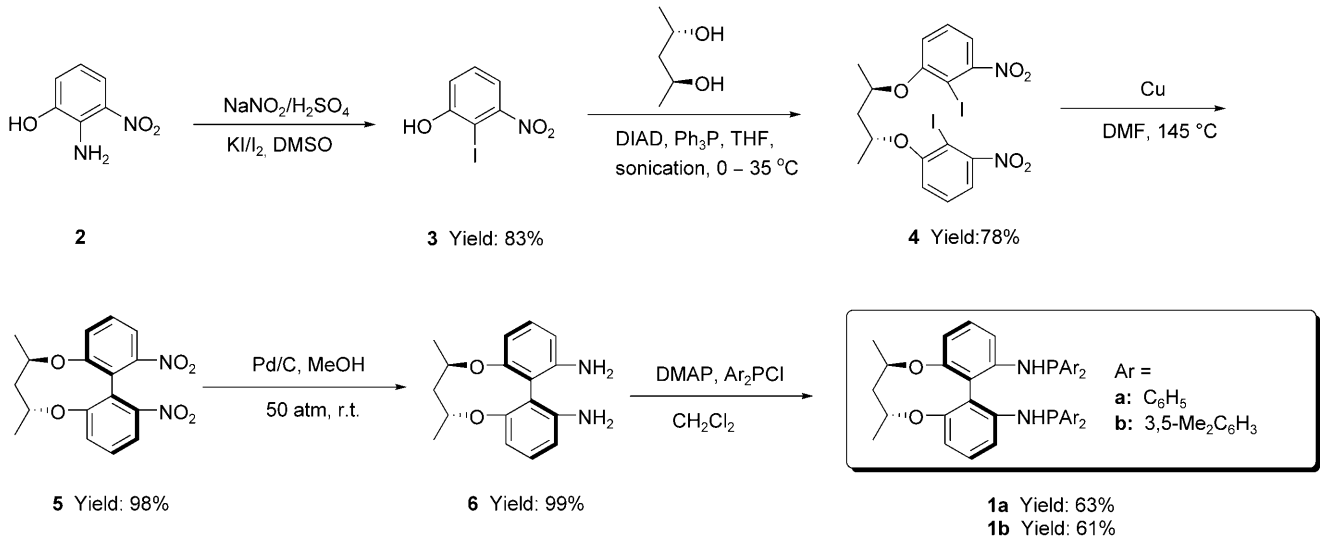
Abstract: A highly efficient strategy for the synthesis of a series of chiral bisaminophosphine ligands was well established with several remarkable features. The synthetic utility of these ligands was explored for rhodium-catalyzed asymmetric hydrogenations of α-dehydroamino acid esters. Up to 98% *ee* values were achieved for the enantioselective synthesis of aminocarboxylic acids and their derivatives, which are very important chiral building blocks for the synthesis of a variety of natural products and biologically active molecules.

Keywords: α-amino acids; asymmetric catalysis; α-dehydroamino acids; enantioselectivity; hydrogenation; rhodium

The increasing demands for enantiomerically pure pharmaceuticals, agrochemicals, and fine chemicals have promoted the development of asymmetric catalytic technologies dramatically.[1] During the last few decades, significant attention has been devoted to the discovery of new catalysts for important asymmetric reactions, such as allylamine isomerization, Michael additions, nucleophilic substitution, alkene carbonylation, etc.[2] Transition metals bound to diverse structures of chiral phosphorus ligands have emerged and become well established as preferential catalysts for asymmetric hydrogenation.[3] In contrast to the broad success in the synthesis and applications of monodentate, C_2-symmetrical or pseudo-C_2-symmetrical bidentate and multidentate phosphorus ligands in asymmetric reactions, only limited results obtained with phosphinite,[4] phosphite,[5] phosphonite,[6] or phosphoroamidite[7] ligands have been reported so far. More recently, Rh catalysts bearing aminophosphine ligands have shown good to excellent enantioselectivities and high reactivities in asymmetric hydrogenation.[8] For example, H_8-BDPAB and BDPAB, reported by Chan, have been successfully applied for hydrogenation of arylenamides.[8g,h] Xyl-BDPAB was also found to be an efficient ligand for the asymmetric hydrogenation of α-dehydroamino acid derivatives.[9] Jiang's bisaminophosphine ligand can be prepared in two steps from C_2-symmetrical (2*R*,3*S*,4*S*,5*R*)-2,5-diamino-1,6-diphenyl-3,4-hexanediol, but only moderate results were observed in the Rh-catalyzed asymmetric hydrogenation.[10]

Recently, Chan's and our groups have introduced central-to-axial chirality transfer in the bisphosphine ligand synthesis with an extremely high diastereomeric aryl-aryl coupling reaction (>99.5%) and several other remarkable features.[11] The presence of additional chiral centers on the ligand backbone was found to exert a significant influence on the enantioselectivity and activity of the catalysts in asymmetric hydrogenations. Herein, as part of our continuing efforts in designing new ligand scaffolds for asymmetric catalysts by using this concept, we have investigated the synthesis and coordination chemistry of modular and fine-tunable chiral bisaminophosphine ligands in anticipation that the resulting phosphines would have different steric and electronic properties. Some asymmetric hydrogenation studies were explored as well.

Scheme 1 depicts the diastereoselective Ullmann coupling reaction for the synthesis of these novel chiral bisaminophosphines **1**. (6*R*,8*R*)-6,8-Dimethyl-1,13-dinitro-7,8-dihydro-6*H*-dibenzo[*f*,*h*][1,5]dioxonine **5** was synthesized in three steps with high yields from readily accessible starting materials as developed by our group.[12] Starting from 2-amino-3-nitrophenol **2**, selective activation of the amino group was achieved



Scheme 1. Synthesis of modular and fine-tunable bisaminophosphine ligands.

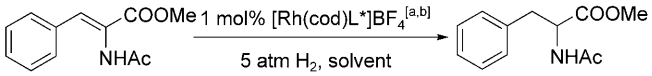
via a one-pot diazotization-iodination sequence to give 2-iodonitrophenol **3** in 83% yield.[13] The chiral bis(nitrophenol ether) **4** was prepared by a Mitsunobu reaction with (2*S*,4*S*)-pentanediol and 2-iodonitrophenol. The double Mitsunobu reaction proceeded smoothly and afforded 78% yield in one hour under sonication conditions. The intramolecular Ullmann reaction of iodides **4**, carried out according to Kornblum and Kendall[14] in DMF, proceeded with surprising ease in a very high yield (up to 98%) and >99% diastereoselectivity based on ^{1}H NMR analysis. The axial chirality *S* was assigned to the intermediate **5** when a crystal suitable for X-ray diffraction was grown and analyzed.[15] Reduction of the nitro groups in intermediate **5** gave the chiral diamine **6** utilizing 5% Pd/C catalyst and at a pressure of 50 atm hydrogen at room tempresure (99% yield). In the presence of 4-dimethylaminopyridine (DMAP) as a hypernucleophilic acylation catalyst, diamine **6** was readily transformed to bisaminophosphine ligands **1a**, **b** in moderate yields after reactions with the corresponding diarylphosphine chlorides.[9]

Several features are highlighted in the synthetic strategy for diaminophosphine ligands. First, the low hindered and strong electron-withdrawing bisnitro groups in compound **4** facilitated the Ullmann coupling reaction, giving the desired intermediate **5** in a very high yield. This strategy circumvents the problem in our initial effort to attach bis(diethyl phosphonate) groups in this step, which led to a relatively low oxidative homo-coupling yield.[11c] Second, the introduction of the synthetically flexible intermediate **6** allows for the convenient divergent incorporation of various aryl substituents of the PAr_2 moieties in the last step. Third, the chiral linking bridge of the 2,4-pentanediol tether is very simple and flexible enough for the chirality transfer from central-to-axial in the Ullmann coupling reaction with complete diastereodifferentiation without unwanted intermolecular coupling; this avoids tedious and time-consuming routine resolutions. Finally, the attractiveness of this ligand class is found in the modular character of the diaminophophine derivatives, which are easily accessible and stable compounds.

To test the synthetic utility of these ligands, we have explored the Rh-catalyzed hydrogenations of α-dehydroamino acid esters. The catalysts **7a**, **b** [Rh(cod)L*]BF_4 (where L* is the chiral ligand **1a**, **b**) were prepared as a reddish brown solid from [$Rh(cod)_2$]BF_4 and the corresponding **1a**, **b** in dichloromethane at room temperature for 20 min. The complexes obtained were used directly in the catalytic reactions.

Asymmetric hydrogenation of α-dehydroamino acid esters demonstrates an efficient approach to access chiral amino acids and their derivatives, which are key structural elements in both natural products and pharmaceuticals.[16] We initiated our studies by screening catalysts **7a**, **b** and solvent systems on the asymmetric hydrogenation of methyl 2-acetamido-3-phenylpropanoate as the model. Under optimized conditions, the reaction was performed at room temperature under 5 atm hydrogen pressure. Both catalysts were found to be effective for this hydrogenation, giving complete conversion over 12 h with 1 mol% catalyst loading. The enantioselectivities achieved in these reactions are shown in Table 1. In the presence of the **7a** complex, up to 97% *ee* and >99% conversion were observed (Table 1, entry 2). The introduction of the somewhat more bulky 3,5-dimethyl (**1b**) groups gave the best enantioselectivity, up to 98% *ee* in methanol (Table 1, entry 8).

Table 1. Ligand and solvent screenings for the asymmetric hydrogenation of methyl 2-acetamido-3-phenylpropanoate **8a**.



8a **9a**

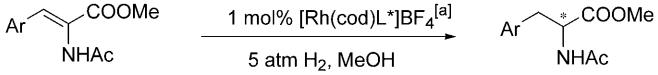
Entry		Solvent	Conv. [%]	*ee* [%][c] (Config.)[d]
1	**1a**	THF	>99	93 (*S*)
2	L*1a	CH_2Cl_2	>99	97 (*S*)
3	**1a**	CH_3OH	>99	95 (*S*)
4	**1b**	acetone	>99	95 (*S*)
5	**1b**	ethyl acetate	>99	91 (*S*)
6	**1b**	toluene	>99	97 (*S*)
7	**1b**	CH_2Cl_2	>99	97 (*S*)
8	**1b**	CH_3OH	>99	98 (*S*)

[a] Unless otherwise noted, the reactions were carried out with S/C = 100.
[b] All reactions were carried out under 5 atm H_2 for 12 h at room temperature.
[c] Enantiomeric excesses were determined by chiral GC using a Chiralsil-Val column.
[d] Absolute configurations of the products were determined by comparing the GC retention times with the reported data in the literature.

Under the optimized reaction conditions, a variety of α-dehydroamino acid esters **8a–l** were examined for hydrogenation (Table 2, entries 1–13). The ligand **1b** system always shows similar or better enantioselectivities than ligand **1a** under the same conditions. All the substrates (Table 2) were reduced to form chiral aminocarboxylic acids with excellent enantioselectivities (93–98%). The electronic and steric nature of a substituent on the phenyl ring of the substrate had little influence on the enantioselectivity and reactivity of the reaction. These enantiomeric excesses were comparable or better in some cases than those obtained when the similar ligand system Xyl-BDPAB or DMBDPPABD was employed.[8g–j] In addition, hydrogenation of the substrate **8c** with a reduced catalyst loading (ligand **1b**, 0.1 mol%) still afforded the corresponding product in full conversion with 96% *ee*. (Table 2, entry 4).

In conclusion, a highly efficient strategy for the synthesis of a series of modular and fine-tunable chiral bisaminophosphine ligands was well established with several remarkable features. The synthetic utility of these ligands was explored for rhodium-catalyzed asymmetric hydrogenations of α-dehydroamino acid esters. Up to 98% *ee* values were achieved for the enantioselective syntheses of aminocarboxylic acids

Table 2. Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid esters.



8a – l **9a – l**

Entry	Substrate	Ar	Product	*ee* [%][b] (Configuration)[c]	
				L1a	**L1b**
1	**8a**	Ph	**9a**	95 (*S*)	98 (*S*)
2	**8b**	3,5-F-C_6H_3	**9b**	94 (*S*)	96 (*S*)
3	**8c**	2-F-C_6H_4	**9c**	96 (*S*)	98 (*S*)
4[d]	**8c**	2-F-C_6H_4	**9c**	n/a	96 (*S*)
5	**8d**	2-Cl-C_6H_4	**9d**	96 (*S*)	96 (*S*)
6	**8e**	2-Br-C_6H_4	**9e**	97 (*S*)	97 (*S*)
7	**8f**	3-Br-C_6H_4	**9f**	93 (*S*)	94 (*S*)
8	**8g**	4-F-C_6H_4	**9g**	96 (*S*)	98 (*S*)
9	**8h**	4-Cl-C_6H_4	**9h**	95 (S)	98 (S)
10	**8i**	4-Br-C_6H_4	**9i**	96 (*S*)	96 (*S*)
11	**8j**	4-CF_3-C_6H_4	**9j**	93 (*S*)	95 (*S*)
12	**8k**	4-MeO-C_6H_4	**9k**	93 (*S*)	96 (*S*)
13	**8l**	4-NO_2-C_6H_4	**9l**	95 (*S*)	95 (*S*)

[a] Unless otherwise noted, the reactions were carried out with S/C = 100; all reactions were carried out under 5 atm H_2 for 12 h at room temperature.
[b] Enantiomeric excesses were determined by chiral GC using a Chiralsil-Val column or chiral HPLC using Chiralcel OD-H column.
[c] Absolute configurations of the products were determined by comparing the GC retention times with the data reported in the literature.
[d] S/C = 1000.

and their derivatives. These significant chiral building blocks find use in the synthesis of a variety of natural products and biologically active molecules.

Experimental Section

General Procedure

To a solution of $[Rh(cod)_2]BF_4$ (6.1 mg, 0.015 mmol) in 4 mL of degassed anhydrous CH_2Cl_2, was added a solution of bisaminophoshine ligand **1** (0.016 mmol) in CH_2Cl_2 (4 mL) at room temperature. The reaction mixture was stirred at room temperature for 20 min before the solvent was removed under vacuum. The resulting complex was used for hydrogenation without further purification. The resulting complex was dissolved in degassed MeOH (15 mL) in the glovebox and was equally distributed into 15 vials. To the catalyst solution was added substrate (0.1 mmol). The vials were transferred into an autoclave, and the autoclave was purged with H_2 (5 atm, for three times) and charged with H_2 (5 atm). After stirring at room temperature for 12 h, the H_2 was carefully released. The reaction solution was purified on a silica gel column to give the corresponding hydrogenation product, which was then directly analyzed by chiral GC or chiral HPLC to determine the enantiomeric excess.

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