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Asymmetric Hydrogenation

A Bisphosphepine Ligand with Stereogenic Phosphorus Centers for the Practical Synthesis of β-Aryl-β-Amino Acids by Asymmetric Hydrogenation**

*Wenjun Tang, Weimin Wang, Yongxiang Chi, and Xumu Zhang**

Enantiomerically pure β-amino acids are important chiral building blocks for the synthesis of β-peptides, β-lactam antibiotics, and many other important chiral drugs.[1] Although chiral β-amino acids have been synthesized through several stoichiometric and catalytic methods,[2] an efficient and practical synthetic method is still needed. The Rh-[3] or Ru-catalyzed[4] asymmetric hydrogenation of β-(acylamino)-acrylic acid derivatives to make chiral β-amino acids has recently attracted much attention. Although many Rh[3] and Ru[4a,c] complexes with chiral phosphane ligands exhibited high enantioselectivities in the hydrogenation of β-alkyl-β-(acylamino)acrylic acid derivatives, the asymmetric hydrogenation of β-aryl-β-(acylamino)acrylic acid derivatives has met with much less success. Heller and co-workers recently reported that the use of a Rh–Et–ferrotane catalyst can give rise to *ee* values of over 99% in the asymmetric hydrogenation of a set of (*E*)-β-aryl-β-(acylamino)acrylic acid derivatives.[3b] However, the preparation of (*E*)-β-aryl-β-(acylamino)acrylic acid derivatives requires their separation from the corresponding thermodynamically more stable *Z* isomers, and low yields are generally observed.[3b] On the other hand, (*Z*)-β-aryl-β-(acylamino)acrylic acid derivatives can be preferentially formed over their *E* isomers under suitable conditions, and high yields for the synthesis of *Z* substrates are attainable.[4b] A highly enantioselective asymmetric hydrogenation of (*Z*)-β-aryl-β-(acylamino)acrylic acid derivatives would allow the practical synthesis of chiral β-aryl-β-amino acids. In previous work we developed a set of Ru–*o*-binapo complexes,[4b] which gave rise to *ee* values of up to 99% in the asymmetric hydrogenation of (*Z*)-β-aryl-β-(acylamino)acrylic acid derivatives.[5] However, the reactivities of the Ru complexes were moderate. A Rh–TangPhos catalyst promoted both high enantioselectivities (up to 98.5% *ee*) and high reactivities in the hydrogenation of a series of *Z* substrates, with the exception of those with *ortho*-substituted β-aryl groups.[3e] Herein we present a new chiral catalyst for the hydrogenation of (*Z*)-β-aryl-β-(acylamino)-acrylic acid derivatives. The Rh complex of the chiral bisphosphepine ligand **1** (abbreviated as (*S*,*S*,*S*)-binapine),

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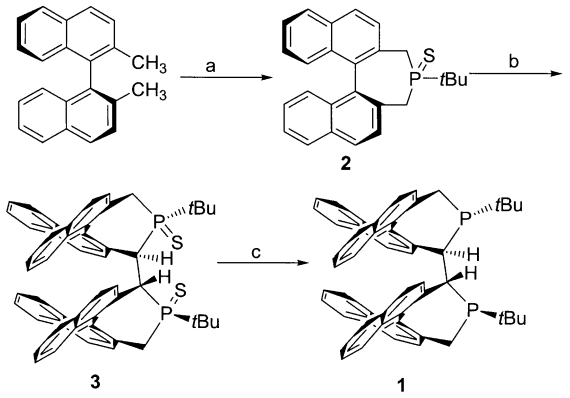
which has stereogenic phosphorus centers, promoted excellent enantioselectivities and reactivities in the asymmetric hydrogenation of a wide range of (*Z*)-β-aryl-β-(acylamino)-acrylic acid derivatives.

Ligand design has played a pivotal role in the development of new efficient metal-catalyzed asymmetric reactions. We recently reported an efficient chiral bisphospholane ligand, TangPhos, with stereogenic P centers, for the asymmetric hydrogenation of various functionalized olefins.[6] In our ongoing efforts toward the development of efficient chiral bisphosphane ligands, we have designed a more rigid chiral bisbinaphthophosphepine ligand, binapine, for use in asymmetric hydrogenation. The structure of ligand **1** not only contains diaxial chirality but also has stereogenic P and C centers. To our knowledge, no chiral bisbinaphthophosphepine ligands with stereogenic P centers have been reported previously.[7] The synthesis of ligand **1** is straightforward (Scheme 1). Double metalation of enantiomerically pure (*S*)-2,2′-dimethylbinaphthyl with *n*BuLi/TMEDA followed by

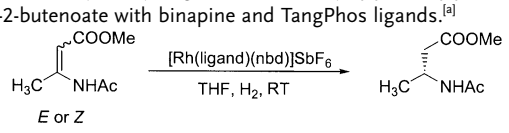


Scheme 1. Synthesis of ligand **1**: a) 1) *n*BuLi, TMEDA, Et_2O; 2) *t*BuPCl$_2$, S, THF, 61%; b) *t*BuLi, TMEDA, HMPA/THF, $CuCl_2$, 25%; c) Si_2Cl_6, benzene, 90%. HMPA = hexamethyl phosphoramide, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

reaction with *t*BuPCl$_2$ and sulfur provided the binaphthophosphepine sulfide **2** in 61% yield.[7c,d] Deprotonation of **2** with *t*BuLi/TMEDA at −78°C in HMPA/THF followed by coupling mediated by $CuCl_2$ yielded **3** as a single isomer in 25% yield, along with recovered starting material **2** (50%). The absolute configuration of **3** was confirmed by its X-ray crystallographic structure.[8] Desulfurization of **3** with hexachlorodisilane[6a] in benzene provided ligand **1** in 90% yield. In its solid state this electron-rich bisphosphane is remarkably insensitive to air. No oxidation product was observed after exposure of the ligand to air for several days. Both isomers of binapine can be synthesized by this simple synthetic route.

Ligand **1** was then used in the Rh-catalyzed hydrogenation of β-(acylamino)acrylic acids. The cationic Rh complex [Rh(**1**)(nbd)]SbF_6 (nbd = 3,5-norbornadiene) was prepared and used directly for the hydrogenation of both the *E* and *Z* isomers of methyl 3-acetamido-2-butenoate (Table 1). In contrast to the Rh–TangPhos catalyst, which promoted the formation of the hydrogenation products from both the *E* and the *Z* substrates with high enantioselectivities, the use of the

Table 1: Rh-catalyzed hydrogenation of methyl (*E*)- and (*Z*)-3-acetylamino-2-butenoate with binapine and TangPhos ligands.[a]

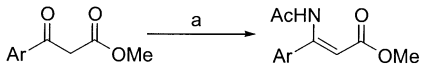


Ligand	Bite angle of Rh complex [°][b]	*ee* [%] from *E* isomer	*ee* [%] from *Z* isomer
(*S*,*S*,*R*,*R*)-TangPhos	75.1	99.6	98.5
1	77.4	32.7	99.2

[a] The absolute configurations of the products were determined as *R* by comparison of their optical rotation data with reported values. The reactions were carried out at room temperature under H_2 (20 psi (138 kPa)) in THF for 24 h. Substrate/[Rh(ligand)nbd]SbF_6 = 100:1. The *ee* values were determined by GC on a chiral phase (Chiralselect 1000 column). [b] Molecular simulations were performed on a CaChe model with MM2 calculations; see Supporting Information for further details.

Rh–binapine catalyst led to superior enantioselectivity for the hydrogenation of the *Z* substrate. However, a low *ee* value was observed for the hydrogenation of the *E* isomer. Molecular simulation on a CaChe model showed that the Rh–binapine complex has a larger P–Rh–P angle (bite angle) than the Rh–TangPhos complex. This difference leads to a sterically more hindered chiral environment in the Rh–binapine complex.

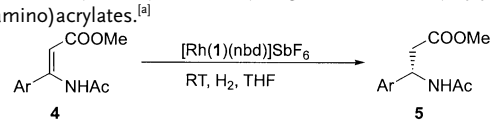
Many chiral β-aryl-β-amino acids are important intermediates for drug synthesis.[9] As a series of (*Z*)-β-aryl-β-(acylamino)acrylic acid derivatives can be obtained in moderate to high yields through the amination of aryl β-keto esters with NH_4OAc, followed by acetylation with acetic anhydride and pyridine at reflux (Scheme 2),[10] the highly



Scheme 2. Synthesis of methyl (*Z*)-β-aryl-β-(acetylamino)acrylates: a) 1) NH_4OAc, CH_3OH; 2) Ac_2O, pyridine, THF, reflux, 50–70% yield of isolated products.

enantioselective hydrogenation of (*Z*)-β-aryl-β-(acylamino)-acrylic acid derivatives could provide a practical method for the synthesis of chiral β-aryl-β-amino acids. We therefore used binapine in the Rh-catalyzed asymmetric hydrogenation of a series of methyl (*Z*)-β-aryl-β-(acetylamino)acrylates. As shown in Table 2, a wide array of chiral β-aryl-β-amino acid derivatives was obtained with *ee* values of over 99%, regardless of the electronic properties of the aryl group on the substrate **4**. Excellent enantioselectivities were also observed in the hydrogenation of substrates with *ortho*-substituted β-aryl groups (Table 2, entries 8 and 9), in contrast to the moderate *ee* values observed when a Rh–TangPhos catalyst was used.[3e] Excellent enantioselectivity was also observed in the hydrogenation of a substrate containing a heteroaryl group. In the presence of HBF_4,[11] the hydrogenation of methyl (*Z*)-β-(3-pyridyl)-β-(acetylamino)acrylate provided the chiral β-(3-pyridyl)-β-amino acid derivative **5j** with 96% *ee* (Table 2, entry 10). **5j** is a key component for the synthesis of the GP IIb/IIIa antagonist RWJ-53308.[9b,c] To further test the catalytic efficiency of the Rh–binapine

Table 2: Rh-catalyzed asymmetric hydrogenation of methyl (*Z*)-β-aryl-β-(acetylamino)acrylates.[a]



Entry	Ar (**4**)	*ee* [%] (**5**)
1	Ph (**a**)	>99 (**a**)
2	*p*-F-Ph (**b**)	>99 (**b**)
3	*p*-Cl-Ph (**c**)	>99 (**c**)
4	*p*-Br-Ph (**d**)	99 (**d**)
5	*p*-Me-Ph (**e**)	>99 (**e**)
6	*p*-MeO-Ph (**f**)	>99 (**f**)
7[b]	*p*-BnO-Ph (**g**)	>99 (**g**)
8	*o*-Me-Ph (**h**)	>99 (**h**)
9	*o*-MeO-Ph (**i**)	99 (**i**)
10[c]	3-pyridyl (**j**)	96 (**j**)

[a] The reactions were carried out at room temperature under H_2 (20 psi (138 kPa)) in THF for 24 h unless otherwise specified. Substrate/[Rh(**1**)(nbd)]SbF_6 = 100:1. The absolute configurations of the products were determined as *S* by comparison of their optical rotation data with reported values. The *ee* values were determined by GC on a chiral phase (Chiralselect 1000 column), unless otherwise specified. [b] The *ee* value was determined by HPLC on a chiral phase ((*S*,*S*)-Whelk-01 column). [c] The hydrogenation was conducted in MeOH in the presence of HBF_4 (1.5 equiv) under H_2 (20 psi (138 kPa)).

catalyst for the asymmetric hydrogenation of β-aryl-β-(acetylamino)acrylates, substrate **4g** was subjected to hydrogenation in the presence of less [Rh(**1**)(nbd)]SbF_6 catalyst (0.1 mol%), and the chiral product **5g** was obtained in quantitative yield and with 99% *ee*.

In conclusion, we have developed a new chiral bisphosphepine ligand with stereogenic phosphorus centers for the asymmetric hydrogenation of (*Z*)-β-(acylamino)acrylic acid derivatives. Excellent enantioselectivities and reactivities were observed in the hydrogenation of a wide array of (*Z*)-β-aryl-β-(acylamino)acrylic acid derivatives. As the substrates for the asymmmetric hydrogenation can be prepared readily, the new ligand binapine provides an efficient method for the practical synthesis of chiral β-aryl-β-amino acids.[12]

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Keywords: asymmetric synthesis · hydrogenation · ligand design · P ligands · rhodium

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[8] CCDC-204741 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or depost@ccdc.cam.ac.uk). We thank Dr. H. Yennawar for solving the crystal structure.

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[10] See Supporting Information for details.

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[12] The Supporting Information includes procedures for the synthesis of and analytical data for binapine, procedures for the synthesis of substrates, hydrogenation procedures, information on molecular simulation, and the X-ray crystal structure of **3**.

