Chiral 1-phenylethylamine-derived phosphine-phosphoramidite ligands for highly enantioselective Rh-catalyzed hydrogenation of β-(acylamino)acrylates: significant effect of substituents on 3,3′-positions of binaphthyl moiety†

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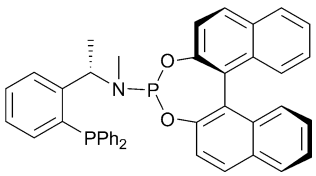
A series of new chiral phosphine-phosphoramidite ligands with a 3,3′-substituted binaphthyl moiety were prepared from 1-phenylethylamine, and successfully applied in the Rh-catalyzed asymmetric hydrogenation of β-(acylamino)-acrylates. The research disclosed that the substituents on the 3,3′-positions of binaphthyl moiety significantly influenced the enantioselectivity.

Chiral β-amino acids are important building blocks in the synthesis of natural products, β-peptides, and pharmaceuticals.[1] Exploring enantioselective methods for the synthesis of optically active β-amino acid derivatives has therefore attracted much attention recently. Due to its inherent efficiency and atom economy, catalytic asymmetric hydrogenation of β-(acylamino)acrylates is arguably one of the most efficient and straightforward ways to β-amino acid derivatives. Indeed, in the past few years, many phosphorus-containing ligands have been reported to exhibit good to excellent enantioselectivities in the Rh- and Ru-catalyzed asymmetric hydrogenation of β-(acylamino)acrylates.[2] However, for most catalytic systems, high enantioselectivities were obtained only when β-alkyl-β-(acylamino)acrylates were used as substrates, whereas the results for the hydrogenation of (*Z*)-β-aryl-β-(acylamino)acrylates, are less satisfying.[2-3] The search for an effective catalytic system for enantioselective hydrogenation of (*Z*)-β-aryl-β-(acylamino)acrylates remains highly desirable.

In the past decade, unsymmetrical hybrid bidentate phosphine-phosphoramidite ligands have emerged as a new, effective ligand class for asymmetric catalysis.[4] In our recent study, we have also found that chiral 1-phenylethylamine-derived phosphine-phosphoramidite ligand, (S_c,S_a)-PEAPhos **1** (Fig. 1), was highly efficient in the Rh-catalyzed asymmetric hydrogenation of various functionalized olefins such as dimethyl itaconate, enamide, and α-dehydroamino acid esters.[5] To further expand its utility in catalytic asymmetric hydrogenation, we attempted to employ this ligand in the Rh-catalyzed asymmetric hydrogenation of (*Z*)-β-aryl-β-(acylamino)acrylates. However, the result disclosed that this ligand was inefficient in this more challenging hydrogenation in terms of enantioselectivity, giving only 71% ee (entry 1, Table 1). We surmised that the relatively flexible features of PEAPhos **1** should answer for this insufficient selectivity, and increasing its steric hindrance by introduction of substituents onto the 3,3′-positions of the binaphthyl moiety of this ligand should improve the enantioselectivity. As a result, we report the synthesis of new phosphine-phosphoramidite ligands **2a-b** with a 3,3′-disubstituted binaphthyl fragment and their application in the Rh-catalyzed asymmetric hydrogenation of β-(acylamino)acrylates, in which significantly improved enantioselectivities (>99% ee) were obtained.



(S_c,S_a)-PEAPhos **1**

Fig. 1 Chiral 1-phenylethylamine derived phosphine-phosphoramidite ligand, (S_c,S_a)-PEAPhos **1**.

The synthesis of new chiral phosphine-phosphoramidite ligands **2a-b** was performed as outlined in Scheme 1. Initially, *N*-methyl-(*S*)-1-[2-(diphenylphosphino)phenyl]ethylamine [(*S*)-DPPNHCH$_3$ **3**] was prepared from (*S*)-1-phenylethylamine through a two-step transformation as we have reported previously.[5-6] The treatment of (*S*)-DPPNHCH$_3$ **3** with (*S*)-3,3′-disubstituted binaphthol derived chlorophosphites **4**[7] in toluene at 0 °C in the presence of 3 equiv of Et$_3$N provided the corresponding phosphine-phosphoramidite ligands **2** in good yields. Similar to the parent ligand **1**, these new ligands **2** also show excellent stability toward air and moisture, and tolerance of various hydrogenation conditions.

With these newly developed phosphine-phosphoramidite ligands in hand, we then examined their efficiency in the Rh-catalyzed asymmetric hydrogenation of (*Z*)-β-aryl-β-(acylamino)acrylates **5**.[8] Initially, ethyl (*Z*)-β-phenyl-β-(acetylamino)acrylate **5a** was used as a model substrate for ligand screening and condition optimizing experiments. All reactions were carried out at room temperature for 24 h in the presence of 1 mol% of catalyst with an Rh : ligand ratio of 1 : 1.1, and the results are summarized in Table 1.

With the parent ligand (S_c,S_a)-PEAPhos **1**, (*Z*)-β-phenyl-β-(acetylamino)acrylate **5a** was hydrogenated to yield the corresponding amino acid ester **6a** in only 71% ee (entry 1). In

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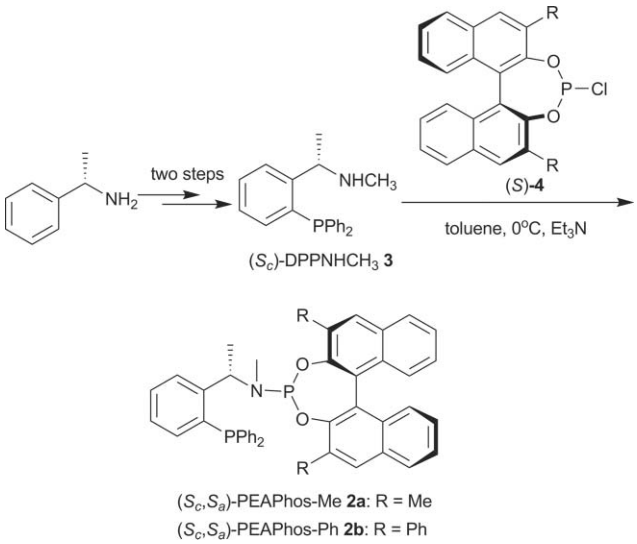
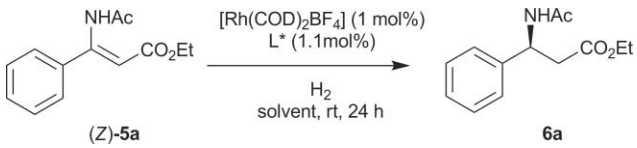


Scheme 1 The synthesis of new chiral phosphine-phosphoramidite ligands (S_c,S_a)-**2a-b**.

Table 1 Rh-catalyzed asymmetric hydrogenation of ethyl (*Z*)-β-phenyl-β-(acetylamino)acrylate **5a**[a]



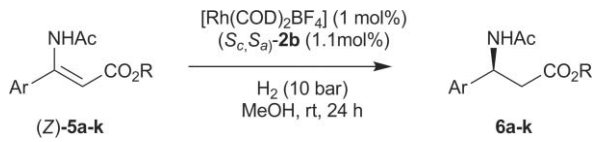
Entry	Ligand	Solvent	H_2/bar	Conv (%)	Ee (%)[b]
1	(S_c,S_a)-**1**	MeOH	20	>99	71
2	(S_c,S_a)-**2a**	MeOH	20	>99	95
3	(S_c,S_a)-**2b**	MeOH	20	>99	>99
4	(S_c,S_a)-**2b**	MeOH	10	>99	>99
5	(S_c,S_a)-**2b**	CH_2Cl_2	10	>99	98
6	(S_c,S_a)-**2b**	Toluene	10	69 (73)[c]	72
7	(S_c,S_a)-**2b**	THF	10	>99	96
8	(S_c,S_a)-**2b**	MeOH	30	53 (48)[c]	99[d]

[a] Hydrogenations were performed in 2 mL of solvent with 0.25 mmol of substrate **5a** and 1 mol% of catalyst prepared *in situ* from $[Rh(COD)_2BF_4]$ and 1.1 equiv of ligand at room temperature for 24 h. [b] Conversions and enantiomeric excesses were determined by chiral GC. [c] Conversions were determined by GC on a DB-17 capillary column using dimethyl phthalate as internal standard substance. The data in parentheses were determined by ^1H NMR. [d] Catalyst loading was 0.1 mol%.

comparison, ligand **2a** with two methyl groups on 3,3′-positions provided an ee-value of 95%, remarkably superior to that obtained with the parent ligand **1** (entry 2). Replacing methyl groups with phenyl groups on the 3,3-positions of the binaphthyl moiety further increased the enantioselectivity to over 99% ee (entry 3). Catalytic asymmetric hydrogenation of (*Z*)-β-aryl-β-(acylamino)acrylates **5** remains a difficult task. Although many ligands have been employed in this transformation, only a few ligands can provide the product in over 95% ee.[2] In 1999, Zhang *et al.* reported the first highly enantioselective hydrogenation of β-(acylamino)acrylates using Rh-BICP and Rh-DuPhos catalytic systems.[8b] However, only moderate enantioselectivities (~65% ee) were obtained with an aryl substituent in the β-(acylamino)acrylates using these catalytic systems. The most important progress was made by the same group in 2003 by using a Rh complex of (*S*,*S*,*S*)-binapine bearing stereogenic phosphorus centers.[8c] By use of this catalytic system, excellent enantioselectivities (>99% ee) and reactivities were obtained in the hydrogenation of a wide range of (*Z*)-β-aryl-β-(acylamino)acrylates. Some other bidentate phosphorus ligands have also been reported to show good to excellent enantioselectivities in this transformation.[4f,9,10] However, no result surpassed that obtained with (*S*,*S*,*S*)-binapine ligand. Therefore, the high enantioselectivity (>99% ee) obtained with the present Rh/(S_c,S_a)-PEAPhos-Ph catalytic system represents one of the best results reported so far.[2] Comparison of the results obtained with **1** and **2a-b** suggested that the steric demand in the 3,3′-positions of the binaphthyl moiety of this phosphine-phosphoramidite ligand class is crucial for achieving high enantioselectivity in this challenging hydrogenation. Lowering H_2 pressure to 10 bar didn't impact the catalytic activity and enantioselectivity (entry 4). The nature of solvent has some influence on the catalytic performance. Thus, the hydrogenation proceeded smoothly in CH_2Cl_2 and THF, giving slightly lower enantioselectivity; while only moderate conversion and enantioselectivity was observed when hydrogenation was performed in toluene (entries 5-7). Reducing the catalyst loading to 0.1 mol% resulted in a dramatically decreased conversion even in a promoted H_2 pressure (30 bar), although high enantioselectivity was maintained (entry 8).

Having established the optimal hydrogenation conditions (1 mol% of catalyst, 10 bar of H_2 pressure and the use of MeOH as solvent), we next investigated the Rh-catalyzed asymmetric hydrogenation of various (*Z*)-β-aryl-β-(acylamino)acrylates **5** with (S_c,S_a)-PEAPhos-Ph **2b**, and the results are summarized in Table 2. In all cases, full conversions were obtained. The results revealed that the substitution pattern of the substituent on the aryl ring of substrates has some effect on the enantioselectivity. For 4- and 3-methyl substituted substrates **5b** and **5c**, the hydrogenation yielded the corresponding β-amino acid esters in over 99% ee

Table 2 Rh-catalyzed asymmetric hydrogenation of (*Z*)-β-aryl-β-(acetylamino)acrylate **5** with (S_c,S_a)-PEAPhos-Ph **2b**[a]

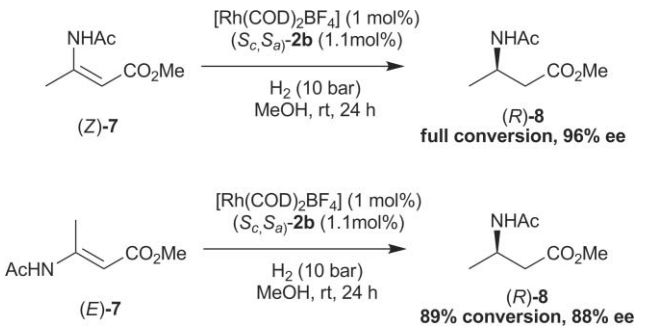


Entry	Substrate (Ar, R)	Ee/% (config)[b]
1	**5a** (Ph, Et)	>99 (*S*)
2	**5b** (4-MeC_6H_4, Me)	>99 (*S*)
3	**5c** (3-MeC_6H_4, Me)	>99 (*S*)
4	**5d** (2-MeC_6H_4, Me)	85 (*S*)
5	**5e** (4-MeC_6H_4, Et)	99 (*S*)
6	**5f** (4-MeOC_6H_4, Me)	99 (*S*)
7	**5g** (4-MeOC_6H_4, Et)	99 (*S*)
8	**5h** (3-MeOC_6H_4, Et)	99 (*S*)
9	**5i** (4-ClC_6H_4, Me)	98 (*S*)
10	**5j** (4-ClC_6H_4, Et)	99 (*S*)
11	**5k** (4-FC_6H_4, Me)	>99 (*S*)

[a] Hydrogenations were performed in 2 mL of MeOH with 0.25 mmol of substrate **5** and 1 mol% of catalyst prepared *in situ* from $[Rh(COD)_2BF_4]$ and 1.1 equiv of ligand **2b** under a H_2 pressure of 10 bar at room temperature for 24 h. Full conversions were obtained in all cases. [b] Enantiomeric excesses were determined by chiral GC (for **6a-e** and **6i-k**) and chiral HPLC (for **6f-h**).

(entries 2-3). However, the hydrogenation of 2-methyl substituted substrate **5d** resulted in dramatically decreased enantioselectivity, providing only 85% ee, which is presumably due to the steric effect as reported by Zhang *et al.* by use of a Rh/TangPhos catalytic system (entry 4).[9] A series of 3- or 4-substituted substrates were then hydrogenated with the present catalytic system, and all of them gave excellent enantioselectivities (entries 5-11). These results demonstrated the high efficiency of this newly developed phosphine-phosphoramidite ligand **2b** in this hydrogenation.

High enantioselectivity was also observed in the Rh-catalyzed asymmetric hydrogenation of (*Z*)-β-alkyl-β-(acylamino)acrylate [(*Z*)-**7**] with (S_c,S_a)-PEAPhos-Ph **2b** (Scheme 2). Unexpectedly, this ligand is not so effective in the hydrogenation of the corresponding (*E*)-β-alkyl-substituted substrate [(*E*)-7], providing incomplete conversion (89% conversion).



Scheme 2 Rh-catalyzed asymmetric hydrogenation of β-alkyl-β-(acylamino)acrylate **7** with ligand **2b**.

In summary, we have prepared some new chiral phosphine-phosphoramidite ligands by the introduction of two substituents onto the 3,3′-positions of the binaphthyl moiety of the (S_c,S_a)-PEAPhos skeleton. These newly developed ligands displayed excellent enantioselectivity in the Rh-catalyzed asymmetric hydrogenation of challenging (*Z*)-β-(acylamino)acrylate substrates, in particular (*Z*)-β-aryl-β-(acylamino)acrylates, giving up to >99% ee. The results also reveal that the presence of the substituents on the 3,3′-positions of the binaphthyl moiety significantly improves the enantioselectivity of this challenging hydrogenation. The further applications of these new ligands in asymmetric catalysis will be disclosed in due time.

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