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Practical Rh(I)-Catalyzed Asymmetric Hydrogenation of β-(Acylamino)acrylates Using a New Unsymmetrical Hybrid Ferrocenylphosphine–Phosphoramidite Ligand: Crucial Influence of an N–H Proton in the Ligand

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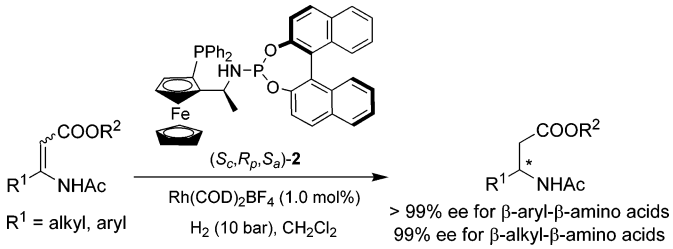
ABSTRACT



Excellent enantioselectivities and high turnovers (S/C = 5000) were achieved in the Rh(I)-catalyzed asymmetric hydrogenation of both β-aryl- and β-alkyl-β-(acylamino)acrylates with a new unsymmetrical hybrid ferrocenylphosphine–phosphoramidite ligand, and the presence of an N–H proton in the ligand was demonstrated to have a crucial role in the enantioselectivity.

Enantiomerically pure β-amino acids and their derivatives are especially attractive due to their vital importance for biochemical and medicinal applications.[1] One of the most convenient and straightforward paths to β-amino acids is the catalytic asymmetric hydrogenation of corresponding prochiral substrates such as β-(acylamino)acrylates. In the past few years, some chiral monodentate and bidentate phosphorus-containing ligands have been reported to show good to excellent enantioselectivity in Rh-[2,3] or Ru-catalyzed[4] asymmetric hydrogenation of β-(acylamino)acrylates. For example, Rh-monophosphoramidite catalysts reported by Feringa et al. hydrogenated (*Z*)-β-alkyl- and β-aryl-β-(acylamino)acrylates in 92−95% ee and (*E*)-β-alkyl-β-(acylamino)acrylates in 98−99% ee.[3a] With Rh-TangPhos, high enantioselectivities (99% ee) were obtained in the hydrogenation of *E*/*Z* isomeric mixtures of both β-alkyl- and β-aryl-β-(acylamino)acrylates.[2g] However, for most catalytic systems, high enantioselectivities can be obtained only when (*E*)-β-alkyl-β-(acylamino)acrylates are used as substrates, while the results of hydrogenation of *Z*-isomers, especially (*Z*)-β-aryl-β-(acylamino)acrylates, are less satisfying. Moreover, in most synthetic protocols for β-(acylamino)acrylates, *Z*-isomers are formed predominantly. Therefore, the develop-

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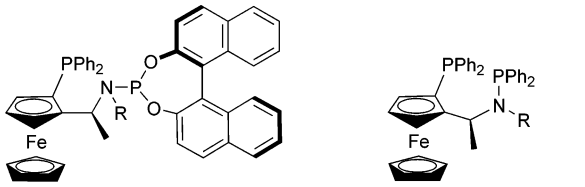
ment of a new catalytic system that can work well for both isomeric substrates, especially for *Z*-isomers, is still needed. Noticeably, nearly all of the successful bidentate *P*-chelate ligands used in this reaction are C_2-symmetrical.[2,4] The C_2-symmetry remains a popular principle in ligand design. However, some quite recent reports have demonstrated the potential of unsymmetrical ligands in the hydrogenation of β-(acylamino)acrylates.[5,6] Due to the high efficiency of monodentate phosphoramidite,[3] an unsymmetrical ligand combining of a phosphine and a phosphoramidite moiety may exhibit good reactivity and selectivity in this reaction.

In our recent research,[7] we have found that the strongly unsymmetrical hybrid ferrocenylphosphine-phosphoramidites (S_c,R_p,S_a)-**1** displayed excellent enantioselectivities in the Rh-catalyzed asymmetric hydrogenation of enamides, dimethyl itaconate and α-dehydroamino acids. To further expand the utility of this unsymmetrical hybrid phosphine-phosphoramidite ligand in asymmetric hydrogenation, we attempted to employ its Rh complex in the hydrogenation of β-(acylamino)acrylates. As a comparison, another kind of unsymmetrical hybrid ligand, Bophoz,[8] having the same chiral ferrocene backbone as (S_c,R_p,S_a)-**1**, was also tested in this reaction (Figure 1). Unfortunately, these ligands exhibited low enantioselectivity in the hydrogenation of β-(acylamino)-acrylates. As shown in Table 1, with Rh/(S_c,R_p,S_a)-**1** complex,

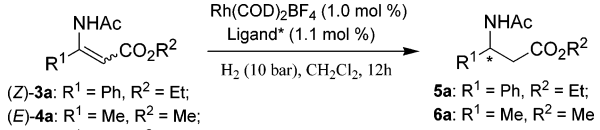


(S_c,R_p,S_a)-**1**: R = Me;
(S_c,R_p,S_a)-**2**: R = H

(S_c,R_p)-**Bophoz-Me**: R = Me;
(S_c,R_p)-**Bophoz-H**: R = H

Figure 1. Ferrocene-based unsymmetrical bidentate phosphorus-containing ligands (S_c,R_p,S_a)-**1**, (S_c,R_p,S_a)-**2**, and Bophoz.

Table 1. Rh-catalyzed Hydrogenation of β-(acylamino)Acrylates Using Unsymmetrical Hydrid Ligand (S_c,R_p,S_a)-**1** and Bophoz[a]



(*Z*)-**3a**: R^1 = Ph, R^2 = Et;
(*E*)-**4a**: R^1 = Me, R^2 = Me;
(*Z*)-**4a**: R^1 = Me, R^2 = Me

5a: R^1 = Ph, R^2 = Et;
6a: R^1 = Me, R^2 = Me

entry	ligand	substrate	% ee[b]
1	(S_c,R_p,S_a)-**1**	(*Z*)-**3a**	65
2	(S_c,R_p,S_a)-**1**	(*E*)-**4a**	24
3	(S_c,R_p,S_a)-**1**	(*Z*)-**4a**	50
4	Bophoz-Me	(*Z*)-**3a**	14
5	Bophoz-Me	(*E*)-**4a**	15
6	Bophoz-Me	(*Z*)-**4a**	38
7	Bophoz-H	(*Z*)-**3a**	64
8	Bophoz-H	(*E*)-**4a**	60
9	Bophoz-H	(*Z*)-**4a**	61

[a] Reactions were performed under 10 bar of H_2 in CH_2Cl_2 at room temperature for 12 h. Substrate/Rh(COD)$_2$BF$_4$/ligand = 100:1:1.1. Full conversions were achieved in all of reactions. [b] Enantiomeric excesses were determined by GC using a chiral Select 1000 capillary (0.25 mm × 30 m) column.

only 65% ee was obtained in the hydrogenation of (*Z*)-**3a** and 50%ee for 4**a** (entries 1−3). The corresponding Bophoz-Me showed much lower enantioselectivity (entries 4−6). However, a significant increase in the enantioselectivity was observed by the use of Bophoz-H with an N−H proton in the ligand (entries 7−9). We then surmised that an N−H proton on the amine unit of the ligand may be crucial to achieving high stereocontrol in the hydrogenation of β-(acylamino)acrylates due to the potential second interaction between the N−H proton in the ligand and substrate.[9] As

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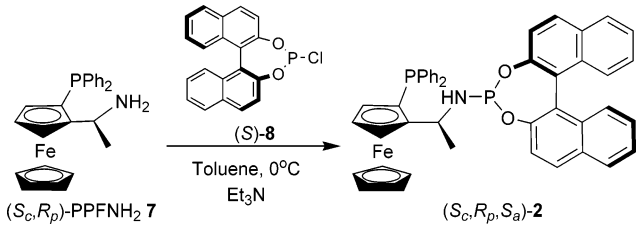
Scheme 1. Synthesis of New Unsymmetrical Hybrid Ferrocenylphosphine−Phosphoramidite Ligands (S_c,R_p,S_a)-**2**

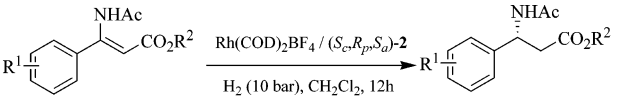


expected, the new ferrocenylphosphine-phosphoramidite ligand (S_c,R_p,S_a)-**2** with an N−H proton is found to show good to excellent enantioselectivities for the hydrogenation of both β-alkyl- and β-aryl-β-(acylamino)acrylates, indicating the crucial influence of an N−H proton on the amine unit in the asymmetric hydrogenation of β-(acylamino)acrylates. Interestingly, our results show, for the first time, that individual hydrogenation of *E*- and *Z*-isomers can be performed under identical catalytic conditions by the use of the same Rh/(S_c,R_p,S_a)-**2** catalytic system, affording β-amino acid derivatives with the opposite configuration and excellent enantioselectivity.

The synthesis of ligand (S_c,R_p,S_a)-**2** is straightforward. By the reaction of (S_c,R_p)-**7**[10] with chlorophosphites **8**[11] in CH_2Cl_2 at 0 °C, ligand (S_c,R_p,S_a)-**2** was prepared in nearly quantitative yields, as outlined in Scheme 1. Similar to its methyl analogues (S_c,R_p,S_a)-**1**, ligand (S_c,R_p,S_a)-**2** also exhibits extraordinary stability toward air and moisture, and tolerance of various hydrogenation conditions, which make this ligand highly practical for general laboratory preparations as well as scale-up operations.

In the first set of experiments, a wide array of (*Z*)-β-aryl-β-(acylamino)acrylates **3** were undertaken to examine the efficacy of this catalyst system for this substrate class. Hydrogenation was conducted under a H_2 pressure of 10 bar in the presence of 1.0 mol % of catalysts prepared in situ from $Rh(COD)_2BF_4$ and 1.1 equiv of chiral ligand (S_c,R_p,S_a)-**2**. Asymmetric hydrogenation of (*Z*)-β-aryl-β-(acylamino)-acrylates remains a challenging task. Recently, some C_2-symmetrical bidentate *P*-ligands such as Binapine[2l] and TangPhos[2g4] have been reported to show excellent enantioselectivity in the Rh-catalyzed hydrogenation of (*Z*)-β-aryl-β-(acylamino)acrylates. We found that the Rh/(S_c,R_p,S_a)-2 system is also very efficient for this type of substrate. As shown in Table 2, excellent enantioselectivity were obtained in each case regardless of the electronic properties of the aryl group on the substrate **3** (entries 2−10). Higher enantioselectivity was obtained in the hydrogenation of ethyl β-aryl-β-(acylamino)acrylates than the corresponding methyl esters, most of ethyl esters were hydrogenated in 99% ee, which is comparable to the best results recently described by Zhang et al. with Rh−Binapine complex (entries 2, 3, 5, 7). The Rh/(S_c,R_p,S_a)-**2** complex showed good performance even at low catalyst loadings (S/C = 5000), providing an ee value of 97% (entry 13). As the substrates can be prepared readily, the Rh/(S_c,R_p,S_a)-**2** system provides an efficient method for the practical synthesis of chiral β-aryl-β-amino acids.

Table 2. Rh-Catalyzed Asymmetric Hydrogenation of (*Z*)-β-Aryl-β-(acylamino)acrylates **3** Using Ligand (S_c,R_p,S_a)-**2**[a]



(*Z*)-**3a**: R^1 = H, R^2 = Et; (*R*)-**5a**: R^1 = H, R^2 = Et;
(*Z*)-**3b**: R^1 = 4-Me, R^2 = Et; (*R*)-**5b**: R^1 = 4-Me, R^2 = Et;
(*Z*)-**3c**: R^1 = 4-Me, R^2 = Me; (*R*)-**5c**: R^1 = 4-Me, R^2 = Me;
(*Z*)-**3d**: R^1 = 4-OMe, R^2 = Et; (*R*)-**5d**: R^1 = 4-OMe, R^2 = Et;
(*Z*)-**3e**: R^1 = 4-OMe, R^2 = Me; (*R*)-**5e**: R^1 = 4-OMe, R^2 = Me;
(*Z*)-**3f**: R^1 = 4-Cl, R^2 = Et; (*R*)-**5f**: R^1 = 4-Cl, R^2 = Et;
(*Z*)-**3g**: R^1 = 4-Cl, R^2 = Me; (*R*)-**5g**: R^1 = 4-Cl, R^2 = Me;
(*Z*)-**3h**: R^1 = 4-F, R^2 = Me; (*R*)-**5h**: R^1 = 4-F, R^2 = Me;
(*Z*)-**3i**: R^1 = 3-OMe, R^2 = Me (*R*)-**5i**: R^1 = 3-OMe, R^2 = Me

entry	substrate	Rh (mol %)	ee (config)[b]
1	(*Z*)-**3a**	1.0	98 (*R*)[c]
2	(*Z*)-**3a**	1.0	>99 (*R*)
3	(*Z*)-**3b**	1.0	98 (*R*)
4	(*Z*)-**3c**	1.0	97 (*R*)
5	(*Z*)-**3d**	1.0	99 (*R*)
6	(*Z*)-**3e**	1.0	98 (*R*)
7	(*Z*)-**3f**	1.0	>99 (*R*)
8	(*Z*)-**3g**	1.0	98 (*R*)
9	(*Z*)-**3h**	1.0	98 (*R*)
10	(*Z*)-**3i**	1.0	98 (*R*)
11	(*Z*)-**3a**	0.1	98 (*R*)
12	(*Z*)-**3f**	0.1	98 (*R*)
13	(*Z*)-**3a**	0.02	97 (*R*)
14	(*Z*)-**3f**	0.02	96 (*R*)

[a] Reactions were performed in the presence of substrate/$Rh(COD)_2BF_4$/ligand = 100:1:1.1 under 10 bar of H_2 in CH_2Cl_2 at 5 °C for 12 h. Full conversions were achieved in all of the reactions. [b] Enantiomeric excesses were determined by GC using a chiral Select 1000 capillary (0.25 mm × 30 m) column. The absolute configuration was determined by comparing the optical rotations with reported values. [c] Reactions were performed at room temperature.

To further show the synthetic utility of this Rh-complex for the synthesis of β-amino acid derivatives, a series of (*Z*)- and (*E*)-β-alkyl-β-(acylamino)acrylates **4** were tested in this reaction. The unsymmetrical hybrid phosphine−phosphoramidite ligand also exhibited good to excellent enantioselectivity for both *Z*- and *E*-isomers. The results are summarized in Table 3. As in most cases,[2,3] the hydrogenation of (*E*)-β-(acylamino)acrylates exhibited higher enantioselectivity than the corresponding *Z*-isomers. It is noted that the sense of enantioselection observed for (*E*)-β-alkyl-β-(acylamino)-acrylates is opposite to that found for *Z*-isomer, which is the first example in the Rh-catalyzed asymmetric hydrogenation of β-(acylamino)acrylates to the best of our knowledge. Thus, the best result was obtained in the hydrogenation of

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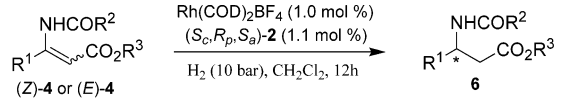
Table 3. Rh-Catalyzed Asymmetric Hydrogenation of β-Alkyl-β-(acylamino)acrylates **4** Using Ligand (S_c,R_p,S_a)-**2**[a]



(*Z*)-**4** or (*E*)-**4**

a: R^1 = Me, R^2 = Me, R^3 = Me;
b: R^1 = Me, R^2 = Me, R^3 = Et;
c: R^1 = Me, R^2 = Ph, R^3 = Me;
d: R^1 = Et, R^2 = Me, R^3 = Me;
e: R^1 = *i*-Pr, R^2 = Me, R^3 = Me

a: R^1 = Me, R^2 = Me, R^3 = Me;
b: R^1 = Me, R^2 = Me, R^3 = Et;
c: R^1 = Me, R^2 = Ph, R^3 = Me;
d: R^1 = Et, R^2 = Me, R^3 = Me;
e: R^1 = *i*-Pr, R^2 = Me, R^3 = Me

entry	substrate	Rh (mol %)	% ee (config)[b]
1	(*Z*)-**4b**	1.0	92 (*S*)[c]
2	(*E*)-**4b**	1.0	92 (*R*)[c]
3	(*Z*)-**4b**	1.0	93 (*S*)
4	(*E*)-**4b**	1.0	97 (*R*)
5	(*Z*)-**4a**	1.0	92 (*S*)
6	(*E*)-**4a**	1.0	98 (*R*)
7	(*Z*)-**4c**	1.0	93 (*S*)[d]
8	(*Z*)-**4d**	1.0	93 (*S*)
9	(*E*)-**4d**	1.0	99 (*R*)
10	(*Z*)-**4e**	1.0	92 (*R*)[e]
11	(*E*)-**4e**	1.0	98 (*S*)[e]
12	(*E*)-**4d**	0.1	95 (*R*)

[a] Reactions were performed under 10 bar of H_2 in CH_2Cl_2 at 5 °C for 12 h. Substrate/Rh(COD)$_2$BF$_4$/ligand = 100:1:1.1. Full conversions were achieved in all of the reactions. [b] Enantiomeric excesses were determined by GC using a chiral Select 1000 capillary (0.25 mm × 30 m) column. The absolute configuration was determined by comparing the optical rotations with reported values. [c] Reactions were performed at room temperature. [d] Enantiomeric excesses were determined by HPLC using a chiralcel OD column. [e] Enantiomeric excesses were determined by GC using a CP-Chiralsil-L-Val capillary (0.25 mm × 25 m) column.

(*E*)-**4d**, providing the hydrogenation product with (*R*)-configuration and an ee value of up to 99% (entry 9). In contrast, the hydrogenation of (*Z*)-**4d** gave the product with (*S*)-configuration and an ee value of 93% (entry 8). When the catalyst loadings were dropped to 0.1 mol %, a decrease in the enantioselectivity to 95% ee was observed (entry 12).

In conclusion, we have found that the unsymmetrical hybrid ferrocenylphosphine−phosphoramidite ligand (S_c,R_p,S_a)-**2** can be highly effective for the Rh(I)-catalyzed asymmetric hydrogenation of β-(acylamino)acrylates, in which an N−H proton on the amine unit of ligands displays a dominant role in the enantioselectivity. Thus, in the hydrogenation of (*Z*)-β-aryl-β-(acylamino)acrylates, excellent enantioselectivity (over 99% ee) was obtained even at low catalyst loadings, which is comparable to the most efficient bidentate *P*-chelate ligands with C_2-symmetry. These results demonstrate that the catalytic performance of the unsymmetrical bidentate *P*-chelate ligands in asymmetric hydrogenation can be equal to that of C_2-symmetrical ligands, challenging the need for C_2-symmetry in ligand design. Interestingly, our research indicates, for the first time, that individual hydrogenation of *E*- and *Z*-isomers can be performed under identical catalytic conditions by the use of the same Rh/(S_c,R_p,S_a)-**2** catalytic system, affording β-amino acid derivatives with the opposite configuration and excellent enantioselectivity. Further investigations of other catalytic asymmetric reactions with these phosphine-phosphoramidite ligands are underway and progress will be disclosed in due time.

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Supporting Information Available: Materials and methods, synthetic procedures for the synthesis of ligand **2**, and methods for the evaluation of enantiomeric excesses of **5** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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