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Published on Web 11/16/2002

Highly Enantioselective Rhodium-Catalyzed Hydrogenation of β-Dehydroamino Acid Derivatives Using Monodentate Phosphoramidites

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Received August 21, 2002

The asymmetric hydrogenation of prochiral olefins is one of the most extensively studied reactions in homogeneous catalysis and is widely applied in the preparation of optically active amino acids, itaconic acids, and amines.[1,2] Despite the successful use of monophosphanes as chiral ligands in the pioneering studies on asymmetric hydrogenation of α-dehydroamino acid derivatives,[3] the field has been dominated for three decades by bidentate chiral ligands,[1,4] considered to be essential to achieve high enantioselectivities in these hydrogenations.[2] However, recent breakthroughs have questioned this common view as chiral monodentate phosphorus ligands can also lead to high enantioselectivities in a number of asymmetric hydrogenations.[4] In the past three years, monophosphines,[5a] monophosphonites,[5b] monophosphoramidites,[5c] and monophosphites[5d] have been successfully used in the enantioselective hydrogenation of α-dehydroamino acids and itaconic acid derivatives,[6] and more recently enamides.[7]

Enantiomerically pure β-amino acid derivatives are important building blocks in the synthesis of β-peptides and β-lactams.[8] One of the most facile routes to β-amino acids involves the asymmetric hydrogenation of the corresponding dehydroamino acid precursors. Although this approach has been widely used for the preparation of α-amino acids, the enantioselective metal-catalyzed hydrogenation of β-(acylamino)acrylates has turned out to be more problematic, mainly because the catalytic behavior is highly dependent on the structure of the substrate (*E* or *Z* isomers, aliphatic or aromatic side chains).[9] To date, these hydrogenation approaches are based on bidentate phosphine or phosphinite complexes with rhodium (BDPMI,[9a] DuPhos,[9c,e] MiniPhos,[9d] BICP,[9e] and BPPM[9g,h]) or ruthenium (BINAPO[9b] and BINAP[9f]). As far as we know, no monodentate ligands have been described for the catalytic asymmetric hydrogenation of β-(acylamino)acrylates.

We now report the use of new monodentate phosphoramidites in the rhodium-catalyzed asymmetric hydrogenation of (*E*/*Z*)-β-dehydroamino acid derivatives leading to excellent (up to 99% ee) enantioselectivities.

A systematic optimization of the structure of MonoPhos (**1**), to enhance both enantioselectivity and activity with this ligand in the dehydroamino acid hydrogenation, initially led to the finding that small R-groups on the amine unit of the ligand (Figure 1) are necessary to achieve high stereocontrol.[5c,10] Further variations of the amine function were introduced by preparing new phosphoramidites [(*S*)-**2** and (*S*,*R*)-**3**], readily obtained starting from (*S*)-MonoPhos [(*S*)-**1**][11] via amine exchange,[12] either with one larger (**2**, Bn) or with one smaller (**3**, H) N-substituent.

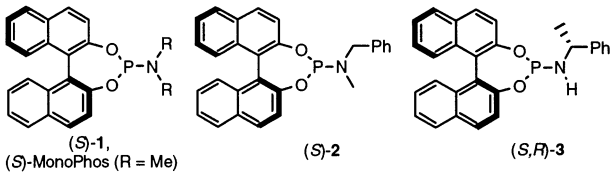

Figure 1. Monodentate phosphoramidites **1**−**3**.

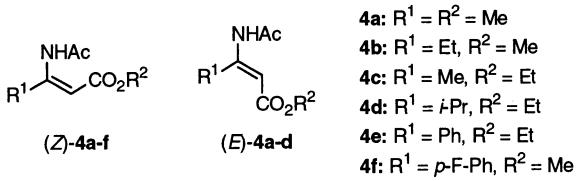

Figure 2. (*E*/*Z*)-β-(Acylamino)acrylates.

To examine the behavior of both ligands, they were first used in the Rh-catalyzed hydrogenation of a benchmark substrate, methyl 2-acetamido cinnamate (*N*-acetyl-dehydrophenylalanine methyl ester).[12] Satisfyingly, under standard conditions,[13] high selectivities were obtained with both ligands. In the case of **2**, the reaction was slightly slower, but the enantioselectivity (95%) was enhanced as compared to that of MonoPhos (**1**) under the same conditions (93% ee). On the contrary, employing ligand **3**, we found that the hydrogenation was dramatically faster, although the enantioselectivity (90%) was somewhat lower as compared to MonoPhos. Remarkably, the ee of the product when using ligand **3** only depends on the chirality of the bisnaphthol unit.[14]

Encouraged by these findings, we decided to study monodentate phosphoramidites **1**−**3** in the hydrogenation of β-dehydroamino acids (Figure 2, Table 1). Substrates **4a**−**f** were prepared according to a known procedure,[9a,b,e,f] allowing the formation of both *Z* and *E* isomers simultaneously (**4a**−**d**) or exclusively the *Z* isomers (**4e**−**f**). These isomers can be separated by silica gel column chromatography.

First, the hydrogenation of the *Z* isomers with aliphatic side chains was examined. Full conversions and 92−95% ee were obtained in the hydrogenation of (*Z*)-**4a**−**d** (entries 6−8 and 10), using 2 mol % of $Rh(COD)_2BF_4$ as catalyst precursor and 2 equiv of ligand (*S*,*R*)-**3** with respect to rhodium in *i*-PrOH under 10 bar of H_2. Remarkably, the hydrogenation of (*Z*)-**4e** and (*Z*)-**4f** under these conditions led to 92% and 94% ee (entries 12 and 13). To the best of our knowledge, this is the highest ee so far reported in the Rh-catalyzed hydrogenation of β-aryl-β-(acylamino)acrylates. The best of all previous reported results is 75.6% ee with BDPMI as ligand.[9a] Recently, up to 99% ee has been reported in the ruthenium-catalyzed hydrogenation of β-aryl-β-dehydroamino acids using bidentate phosphinite ligands.[9b] During the optimization

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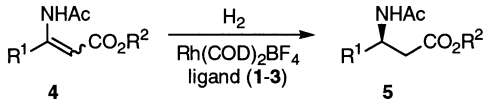
10.1021/ja028235t CCC: $22.00

Table 1. Asymmetric Hydrogenation of (*E*/*Z*)-**4**



4 **5**

entry	**4**	ligand	solvent	cat (%)	*p* (bar)	time (h)	conv (%)[c]	ee (%)[d]
1[a]	(*Z*)-**4a**	**3**	EtOAc	1	1	24	88	3
2[a]	(*Z*)-**4a**	**3**	*i*-PrOH	1	1	24	98	20
3[a]	(*Z*)-**4a**	**3**	*i*-PrOH	1	1	3	40	47
4[a]	(*Z*)-**4a**	**3**	*i*-PrOH	1	10	16	100	77
5[b]	(*Z*)-**4a**	**3**	*i*-PrOH	1	10	1	100	**94**
6[b]	(*Z*)-**4a**	**3**	*i*-PrOH	2	10	0.3	100	**95**
7[b]	(*Z*)-**4b**	**3**	*i*-PrOH	2	10	0.3	100	**94**
8[b]	(*Z*)-**4c**	**3**	*i*-PrOH	2	10	0.3	100	**94**
9[b]	(*Z*)-**4c**	**3**	*i*-PrOH	0.5	10	1	100	**94**
10[b]	(*Z*)-**4d**	**3**	*i*-PrOH	2	10	0.3	100	**92**
11[b]	(*Z*)-**4d**	**3**	*i*-PrOH	2	25	0.05	100	**92**
12[b]	(*Z*)-**4e**	**3**	*i*-PrOH	2	10	0.3	100	**92**
13[b]	(*Z*)-**4f**	**3**	*i*-PrOH	2	10	0.3	100	**94**
14[a]	(*E*)-**4a**	**3**	*i*-PrOH	1	10	18	52	52
15[a]	(*E*)-**4a**	**3**	CH_2Cl_2	1	10	18	100	83
16[a]	(*E*)-**4a**	**1**	*i*-PrOH	1	10	18	49	64
17[a]	(*E*)-**4a**	**1**	CH_2Cl_2	1	10	18	100	95
18[a]	(*E*)-**4a**	**2**	CH_2Cl_2	1	10	18	86	**98**
19[b]	(*E*)-**4a**	**2**	CH_2Cl_2	2	10	4	100	**99**
20[b]	(*E*)-**4b**	**2**	CH_2Cl_2	2	10	4	100	**99**
21[b]	(*E*)-**4c**	**2**	CH_2Cl_2	2	10	4	100	**98**
22[b]	(*E*)-**4c**	**2**	CH_2Cl_2	2	25	3	100	**99**
23[b]	(*E*)-**4c**	**2**	CH_2Cl_2	0.5	25	6	100	**98**
24[b]	(*E*)-**4d**	**2**	CH_2Cl_2	2	10	4	100	**99**

[a] The reaction was performed at room temperature by dissolving **4**, $Rh(COD)_2BF_4$, and ligand (100:1:2) in the suitable solvent. [b] A solution of $Rh(COD)_2BF_4$ and 2 equiv of ligand in CH_2Cl_2 (10 mM) was added to the reaction mixture. [c] Determined by ^1H NMR. [d] Determined by chiral GC. The configuration of the product is *R* (**5a**−**d**) and *S* (**5e**−**f**). See Supporting Information for details. For the absolute configuration of the ligands, see Figure 1.

process, several observations were made: (1) A protic solvent leads to an important increase in the enantioselectivity (compare entries 1 and 2).[15] (2) At low hydrogen pressure, the ee decreases during the reaction (entries 2 and 3). (3) Higher hydrogen pressure results in a considerable increase in the enantioselectivity (entries 3 and 4).[16] (4) A dramatic increase in the reaction rate (TOF up to 1000 h^{-1}, entry 11) and in the ee of the product is obtained when a preformed solution of both catalyst precursor and ligand in CH_2Cl_2 is added to the reaction mixture (entries 4 and 5). Under these conditions, it is possible to reduce the amount of catalyst while maintaining the same enantioselectivity (TON = 200, entry 9).

In contrast to the results with the *Z* isomers, when studying the hydrogenation of (*E*)-**4a**−**d**, ligand (*S*)-**2** turned out to be the most efficient, affording excellent enantioselectivities (98−99% ee, entries 19−21 and 24) when using 2 mol % of $Rh(COD)_2BF_4$ as catalyst precursor and 2 equiv of ligand **2** with respect to rhodium in CH_2Cl_2 under 10 bar of H_2. In this case, it was observed that by using a nonprotic solvent, better conversion and enantioselectivity were obtained as compared to a protic solvent (entries 14 vs 15 and 16 vs 17). As in the *Z* series, the rate of the reaction and the ee of the product were improved when a preformed solution of both catalyst precursor and ligand in CH_2Cl_2 was added to the reaction mixture (entries 18 and 19). Remarkably, at higher hydrogen pressure, the same ee was reached (entry 21 and 22).[16] Under these conditions, it was also possible to reduce the amount of catalyst while maintaining the same enantioselectivity (entry 23).

In conclusion, new and readily accessible monodentate phosphoramidite ligands (**2** and **3**) have been developed that lead to excellent ee's and full conversions in the hydrogenation of (*E*)- and (*Z*)-β-dehydroamino acid derivatives with both aliphatic and aromatic side chains. Particularly, two different catalytic systems have been established for *E* (up to 99% ee) and *Z* (up to 95% ee) isomers, based on the very easy fine-tuning of monophosphoramidites leading to selectivities comparable to or better than those reached with bidentate ligands reported so far.

Acknowledgment. We thank Mr. M. B. van Gelder and Mr. E. P. Schudde for technical support and Mr. M. van den Berg, Dr. J. A. F. Boogers, and Dr. A. H. M. de Vries for useful discussions. D.P. also thanks the European Community (IHP Program) for the award of a Marie Curie Fellowship (contract no. HPMF-CT-2002-01612).

Supporting Information Available: Experimental and chromatographic details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Other authors (see ref 7b) recently also described the beneficial influence of small alkyl groups on the nitrogen.

(11) MonoPhos (**1**) was prepared from bis-β-naphthol and HMPT with excellent yields: Hulst, R.; de Vries, N. K.; Feringa, B. L. *Tetrahedron: Asymmetry* **1994**, *5*, 699.

(12) See Supporting Information.

(13) With 5% of $Rh(COD)_2BF_4$ as the catalyst precursor, 11% of the monodentate ligand in EtOAc at room temperature, and 1 bar of H_2.

(14) Although the diastereoisomer (*S*,*S*)-**3** seems to be less stable than (*S*,*R*)-**3**, both led to a similar ee. This result is analogous to one reported by Reetz and Mehler in the case of monophosphites (see ref 5d).

(15) It is known that polar solvents favor the hydrogenation of (*Z*)-β-(acylamino)acrylates probably because these solvents can break up the intramolecular hydrogen bond in the substrate and thus allow a selective bidentate coordination to the metal (see ref 9a and f).

(16) Interestingly, it has been reported that in the case of bidentate phosphines, the ee decreases upon increasing the pressure (see ref 9a and c).

JA028235T