Rhodium/MonoPhos-Catalysed Asymmetric Hydrogenation of Enamides

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Dedicated to Professor Roger Sheldon on the occasion of his 60th birthday.

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de or from the author.

Abstract: The monodentate phosphoramidite MonoPhos has been used in the rhodium-catalysed asymmetric hydrogenation of *N*-acetyl-α-arylenamides. This ligand is readily available *via* a one-step procedure and is air stable. Its Rh(I) complex, which is an effective catalyst precursor for the hydrogenation of dehydroamino acids, also gives high enantioselectivities for this class of substrates. Because of the facile synthesis and stability of MonoPhos, its complex provides a general solution in preparing chiral amine derivatives through asymmetric hydrogenation.

Keywords: asymmetric catalysis; chiral amines; enamides; enantioselective hydrogenation; homogeneous; phosphoramidites; rhodium

Introduction

Transition metal-catalysed asymmetric hydrogenation is a highly efficient and practical way of introducing chirality.[1,2,3,4] The introduction of this new asymmetric hydrogenation methodology for the industrial preparation of homochiral building blocks and intermediates is seen to proceed at a steady pace. Extensive research has been performed since the first publications in 1968 by Knowles and Horner.[5,6] In olefin hydrogenation the emphasis has been on the development of new chiral ligands and catalysts for the reduction of functionalised prochiral olefins, in particular to afford optically active amino acids. For recent examples of highly enantioselective reduction of non-functionalised olefins see the work of Pfaltz[7,8] and Buchwald.[9] The asymmetric hydrogenation of enamides has been studied to a limited extent although it would provide a highly attractive means to produce chiral amines. One of the first examples of the asymmetric hydrogenation of an α-arylenamide was reported by Kagan et al. employing a complex of rhodium, with DIOP as a bidentate ligand, to afford ee's up to 92%.[10] Higher enantioselectivities were obtained with chiral phosphine ligands like DuPHOS, BPE,[11,12,13] CDP,[14] BICP,[15] Binaphane,[16], DIOP analogues,[17,18] bdpmi,[19] PennPhos,[20] aminophosphine BDPAB,[21] bisphosphinite spirOP[22] and TangPhos.[23,24] Bidentate ligands which can chelate rhodium were used in all these studies with the majority being chiral diphosphines. The limited number of studies on the asymmetric hydrogenation of α-arylenamides suggests that this is a class of substrates which is more difficult to hydrogenate with high enantioselectivity. Recently, we and others have shown that bidentate ligands are not a prerequisite to obtain high enantioselectivities in the hydrogenation of dehydroamino acids. Monodentate phosphonites,[25] phosphites[26] and phosphoramidites[27] can also be used to achieve excellent levels of chiral induction. Major advantages of, for instance, monodentate phosphoramidites are that these ligands are easy to prepare in 1 ~ 2 chemical steps and that they are stable towards air, unlike most phosphines, which adds to the practicality of catalysts based on these ligands. Herein we report the use of a monodentate phosphoramidite ligand, MonoPhos **1**, in the asymmetric hydrogenation of α-arylenamides. This study demonstrates for the first time that primary amine derivatives can be obtained with high enantioselectivities using chiral hydrogenation catalysts based on cheap and readily accessible monodentate ligands.

Results and Discussion

The rhodium-catalysed asymmetric hydrogenation of enamides (Scheme 1) was examined using the phos-

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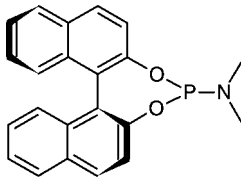

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Figure 1. Monodentate phosphoramidite ligand MonoPhos **1**.[27,30]

phoramidite ligand (*S*)-MonoPhos **1**, previously shown to be highly effective in asymmetric hydrogenation of dehydroamino acids.

The enamide substrates **3**–**7** and **10** (Figure 2) were prepared following literature procedures (Scheme 2).[13,20,28] The stereochemistry of **5** and therefore of **6** was determined by X-ray diffraction analysis.[29] The heteroaromatic enamides **8** and **9** were synthesised using a modified literature procedure[11] starting from the corresponding aryl nitriles (Scheme 2). (*S*)-MonoPhos **1** was prepared as described earlier from (*S*)-bis-β-naphthol and HMPA.[27,30] The actual catalyst was prepared *in situ* from the precursor $Rh(COD)_2BF_4$ and two equivalents of MonoPhos **1** as the chiral ligand in ethyl acetate or dichloromethane.

The hydrogenation reactions were performed in an autoclave with magnetic stirring under a H_2 pressure of 15 bar. We were pleased to see that the parent substrate **3** could be hydrogenated at room temperature to provide the corresponding *N*-acetylamine in 100% yield with an enantioselectivity of 86%. The enantioselectivity improved to 90% by lowering the temperature to −5 °C. Furthermore it is noted that using dichloromethane as a solvent, slightly higher ee's are obtained compared to ethyl acetate as a solvent (Table 1, entries 1, 2 *vs.* 3, 4). To investigate the scope of this asymmetric hydrogenation various enamides were studied (Figure 2). The results of hydrogenation both in ethyl acetate and dichloromethane are summarised in Table 1. The complex of rhodium and MonoPhos is capable of hydrogenating a variety of α-arylenamides with modest to high levels of enantioselectivity. Heteroaromatic α-enamides **8** and **9** (entries 20–27) are hydrogenated with comparable results as seen in the hydrogenation of **3**. The highest enantioselectivity is found for substrate **9** in dichloromethane at −5 °C providing the corresponding *N*-acetylamine with 94% ee (Table 1, entry 25). Halogen substitution at the aromatic ring (substrate **4**) affords similar results when compared with **3**, but the additional chloride substituent provides a means to subsequently functionalise the product *via* a palladium catalysed cross-coupling reaction. From entries 9 and 13 it becomes evident that the introduction of an ethyl substituent at the olefinic moiety has a large influence on the enantioselectivity in the hydrogenation.

Substrate **5**, having a *Z* configuration at the alkene, affords the product in high enantioselectivity but substrate **6**, with an *E* configuration, yields a substantially lower ee in the hydrogenation product. Besides the lower selectivity the conversion of *E*-**6** is also much slower when compared to substrate *Z*-**5**; a finding which contrasts with examples reported in the literature,[13,31] for which high levels of ee were observed in the hydrogenation of mixtures of *E* and *Z* enamides. Furthermore it was found that the hydrogenation of *E*-isomer **6** in dichloromethane at 25 °C was accompanied by isomerisation of the olefinic double bond during the reaction yielding *Z*-**5**. This isomerisation was not

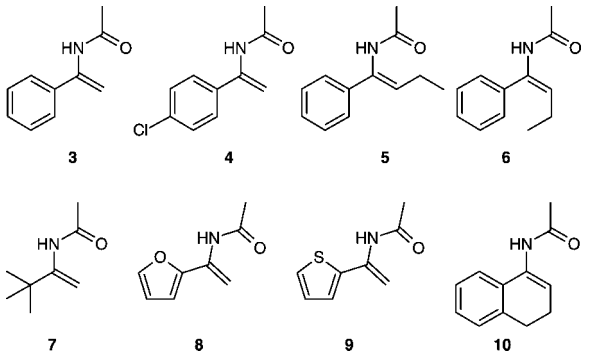
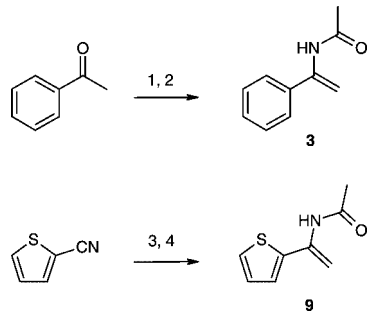
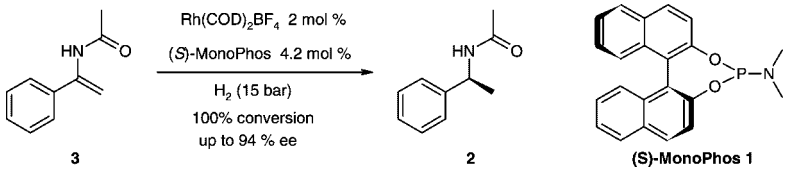


Figure 2. *N*-Acetyl-α-arylenamide substrates.

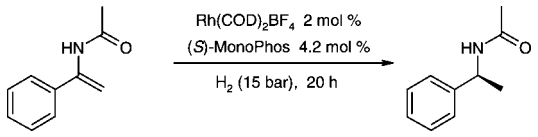


Scheme 2. Synthesis of substrates;[11,13,20,28] 1: H_2NOH HCl, EtOH, pyridine; 2: Ac_2O, AcOH, Fe, TMSCl, toluene; 3: MeMgBr, Et_2O; 4: Ac_2O, Et_2O.



Scheme 1. Hydrogenation using monodentate phophoramidite MonoPhos **1**.

Table 1. Rh-catalysed asymmetric hydrogenation of various *N*-acetyl-α-arylenamides.[a]



3 **2**

Entry	Substrate	Solvent	T [°C]	Conversion [%][b]	ee [%][c]	Configuration[d]
1	**3**	DCM	25	100	86	*S*
2	**3**	DCM	−5	100	**90**	*S*
3	**3**	EtOAc	25	100	74	*S*
4	**3**	EtOAc	−5	100	87	*S*
5	**4**	DCM	25	100	89	*S*
6	**4**	DCM	−5	100	**92**	*S*
7	**4**	EtOAc	25	100	73	*S*
8	**4**	EtOAc	−5	100	**93**	*S*
9	**5**	DCM	25	100	84	*S*
10	**5**	DCM	−5	47	89	*S*
11	**5**	EtOAc	25	100	63	*S*
12	**5**	EtOAc	−5	52	87	*S*
13	**6**	DCM	25	11	24	*S*
14	**6**	EtOAc	25	58	15	*S*
15	**6**	EtOAc	−5	24	26	*S*
16	**7**	DCM	25	80	43	*S*[e]
17	**7**	DCM	−5	45	43	*S*[e]
18	**7**	EtOAc	25	63	24	*S*[e]
19	**7**	EtOAc	−5	62	36	*S*[e]
20	**8**	DCM	25	100	85	*S*
21	**8**	DCM	−5	100	**92**	*S*
22	**8**	EtOAc	25	100	69	*S*
23	**8**	EtOAc	−5	23	72	*S*
24	**9**	DCM	25	100	**90**	*S*
25	**9**	DCM	−5	100	**94**	*S*
26	**9**	EtOAc	25	100	81	*S*
27	**9**	EtOAc	−5	22	**93**	*S*
28	**4**	DCM	25	100	89	*S*[f]
29	**10**	DCM	25	52	35	–[g]

[a] The reaction conditions were $Rh(COD)_2BF$:MonoPhos:substrate = 0.02:0.042:1, H_2 pressure 15 bar, reaction time 20 h, although most reactions gave full conversion in within 4 h.
[b] Conversion to product determined by ^1H NMR and GC analysis.
[c] Determined by chiral GC, see experimental section.
[d] Absolute configurations were assigned by analogy, through chiral GC elution order with an enantiopure sample of *N*-acetylphenylethylamine.
[e] Absolute configurations were assigned by analogy, through chiral GC elution order according to literature.[13]
[f] Reaction time of one hour.
[g] Not determined.

observed in ethyl acetate or at lower reaction temperatures. Enamide **7** with a *t*-Bu group could be hydrogenated in moderate to good yield, although with disappointing ee. Further research is needed to elucidate if the low ee is due to steric hindrance of the bulky *t*-Bu group or due to the presence of an aliphatic group instead of an aromatic one which changes the electronic properties of the enamide. After the hydrogenation of **7**, NMR revealed acetamide present in the reaction mixture. When a substrate was used with the double bond in a six-membered ring (dehydronaphthalene derivative **10**) a slow reaction rate and moderate selectivity were found (entry 29). Compared to **6**, the incorporation of the olefinic double bond in a six-membered ring does not seem to have a major influence on the asymmetric hydrogenation reaction.

Conclusion

Catalytic hydrogenation of *N*-acetyl-α-arylenamides using $Rh(COD)_2BF_4$ and MonoPhos results in full conversions and high ee's. Halogen substituents on the phenyl ring do not give any problems when compared to

the unsubstituted substrate neither are there any problems when the phenyl is replaced by a heteroaromatic ring. The substitution pattern and the configuration at the olefinic double bond on the other hand have an influence on the hydrogenation. Whereas the *Z*-isomer gives similar results to substrate **3**, the *E*-isomer has a lower conversion and enantioselectivity. The hydrogenation of *t*-Bu-substituted enamides poses a problem for this catalytic system as lower enantioselectivities are obtained. Although some diphosphines clearly result in higher ee's in the hydrogenation of *N*-acetyl-α-arylenamides, we have shown that bidentate ligands are not a prerequisite for the hydrogenation of *N*-acetyl-α-arylenamides as well. Most notable the readily accessible monodentate phosphoramidite MonoPhos can also be used to obtain full conversions and high ee's.

Experimental Section

General Remarks

All reactions were performed in a dry nitrogen atmosphere using standard Schlenk techniques. Solvents were reagent grade and dried and distilled before use following standard procedures. NMR spectra were recorded at room temperature in $CDCl_3$ on Varian Gemini 200 (200 MHz) or Varian VXR 300 (300 MHz) spectrometers. Chemical shifts were determined relative to the residual solvent peak. Enantiomeric excesses were determined by capillary GC analysis on an HP 5890 with a Supelco β-Dex 120 column (30.0 m × 250 μm × 0.25 μm) and on an HP 6890 with Chrompack Chirasil-L-Val (25.0 m × 250 μm × 0.25 μm) or Chirasil-Dex CB column (25.0 m × 250 μm × 0.25 μm), with helium as carrier gas. HPLC analyses were performed using a Chiralcel-OD column (250 mm × 4.6 mm), with *n*-heptane/2-propanol as mobile phase (98:2, 1 mL/min) and detection by a diode array UV/Vis detector.

General Procedure for the Synthesis of *N*-Acetyl-α-arylenamides 3 – 7 and 10[13,20,28]

Acetophenone (11.7 mL, 100 mmol) and hydroxylamine hydrochloride salt (14.8 g, 213 mmol) were dissolved in ethanol (150 mL) and pyridine (15 mL). After refluxing for 5 h the solvent was evaporated and water (150 mL) was added before the solution was cooled while stirring in an ice bath. The precipitate was filtered and washed with ice/water (50 mL) before being dissolved in ethyl acetate, dried over $MgSO_4$, and the solvent evaporated under reduced pressure. No further purification was required for the next step.

To a solution of the resulting oxime (12.4 g, 92 mmol) in toluene (135 mL), Ac_2O (26.1 mL, 276 mmol), AcOH (10.3 mL, 276 mmol), Fe (10.8 g, 193 mmol, Aldrich – 325 mesh), and a few drops of TMSCl were added. After stirring at 70 °C for 5 hours the mixture was cooled to room temperature and filtered over Celite®, washed with toluene (2 × 30 mL) and NaOH (2 M, 2 × 135 mL), dried over $MgSO_4$, and the solvent evaporated under reduced pressure. The products were purified by recrystallisation from ethyl acetate. Spectral data of 3 - 7 and 10 were in agreement with those reported in literature.[13,20]

General Procedure for the Synthesis of *N*-Acetyl-α-arylenamides 8 and 9[11]

To a stirred solution of MeMgBr (6 mL, 3 M solution in Et_2O) diluted with Et_2O (20 mL) was added dropwise a solution of ArCN (17 mmol) in Et_2O (10 mL). The mixture was heated at reflux overnight until all the starting material was converted (as indicated by TLC). Subsequently, a solution of acetic anhydride (1.60 mL, 17 mmol) in Et_2O (20 mL) was added dropwise and the mixture was heated at reflux overnight. After cooling to room temperature, methanol was added until all salts were dissolved (35 mL). Water (50 mL) was added and the reaction mixture was extracted with EtOAc (3 × 50 mL). The combined extracts were washed with brine, dried over $MgSO_4$, and the solvent evaporated under reduced pressure. The products were purified by column chromatography using silica gel and a mixture of ethyl acetate and hexane as the eluent. Spectral data of **8** and **9** were in agreement with those reported in literature.[11]

General Procedure for the Asymmetric Hydrogenation of *N*-Acetyl-α-arylenamides 3 – 10

In an autoclave with seven small glass tubes equipped with magnetic stirrers, the glass tubes were charged with substrate (120 μmol), $Rh(COD)_2BF_4$ (0.97 mg, 2.40 μmol), MonoPhos (1.81 mg, 5.04 μmol) and CH_2Cl_2 (3 mL). The autoclave was purged three times with nitrogen and two times with hydrogen before being pressurised with H_2 to 15 bar. The solution was stirred (20 h) at room temperature. The resulting solution was passed through a small plug of silica gel using ethyl acetate as the eluent. The conversion of the reaction and the ee of the product were determined by GC or HPLC.

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