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Modified BINAPO ligands for Rh-catalysed enantioselective hydrogenation of acetamidoacrylic acids and esters

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Abstract—(*S*)- and (*R*)-2,2′-Bis[bis(3,5-dimethylphenyl)phosphinoyl]-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl (Xyl-H_8-BINAPO) were synthesised by reacting chlorobis(3,5-dimethylphenyl)phosphine with (*S*)- and (*R*)-2,2′-dihydroxyl-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl, respectively. The applications of these ligands and their corresponding parent analogues in the Rh-catalysed asymmetric hydrogenation of a variety of acetamidoacrylic acids and esters provided chiral amino acid derivatives with good to excellent ee's (up to 97%). © 2002 Published by Elsevier Science Ltd.

1. Introduction

The diphenylphosphinyl group (PPh_2) is an important functional moiety in chiral ligands for catalytic asymmetric reactions.[1] The stereochemical influence is usually conferred from the backbone chirality to PPh_2 by inducing face–edge interactions between the two phenyl groups.[2] However, these interactions do not always give the desired results. Ligand optimisation, without altering the backbone structure, by introducing various substituents onto the phenyl rings (especially at the *meta*-positions) may perturb the original face–edge interactions of the parent moiety to create a more rigid chiral pocket and lead to interesting and/or improved results. Reports in the literature espouse this special '3,5-dialkyl *meta* effect', for instance, in asymmetric Heck reactions,[3] hydrogenations,[3,4] hydrocyanations[5] and hydroborations.[6]

As a result of the steric and electronic modulation in the H_8-binaphthyl skeleton, some chiral ligands derived from it exhibit higher efficiency and enantioselectivity in asymmetric catalytic reactions than those shown by their parent counterparts.[7] For example, 2,2′-bis(diphenylphosphinoyl)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl (H_8-BINAPO) provided greater enantioselectivities in the Rh-catalysed asymmetric hydrogenation of amidoacrylic acids and esters than the unmodified 2,2′-bis(diphenylphosphinoyl)-1,1′-binaphthyl (BINAPO).[7a]

In this study, we were interested in enhancing the performance of the BINAPO ligand series in the enantioselective hydrogenation of acetamidoacrylic acids and esters by *dual modulations in the binaphthylene structure and the diarylphosphinyl groups*.

2. Results and discussion

2.1. Synthesis of ligands

The ligands (**3** and **4**) to be examined were synthesised by reacting the chlorobis(3,5-dimethylphenyl)-phosphine with (*S*)-BINOL or (*S*)-H_8-BINOL in the presence of catalytic amount of 4-*N*,*N*-dimethylaminopyridine and dry triethylamine in dichloromethane under a nitrogen atmosphere at 0°C (Scheme 1). Chromatographic purifications afforded the diphosphinites in analytically pure forms. Both antipodal forms can be obtained via this method by starting from the corresponding BINOL and H_8-BINOL.[8]

2.2. Rh-catalysed enantioselective hydrogenation of prochiral acetamidoacrylic acids and esters

The cationic rhodium catalysts (**A**: [Rh(*S*)-**3**(COD)]BF_4, **B**: [Rh(*S*)-**4**(COD)]BF_4) were prepared in situ by reacting the appropriate ligand with

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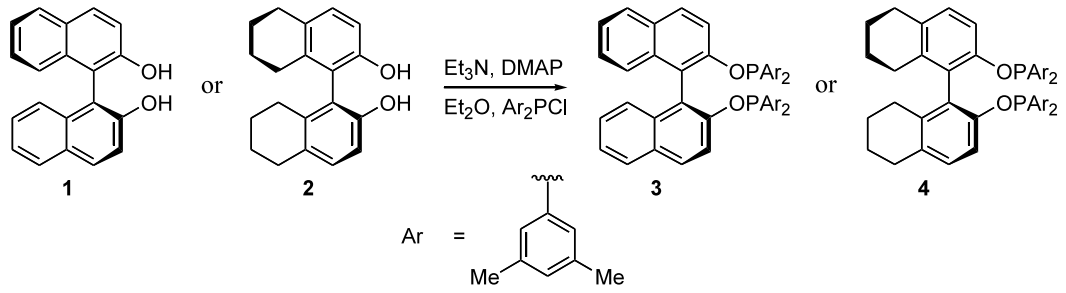


Scheme 1.

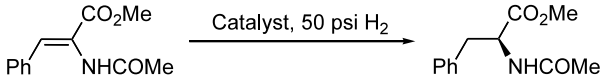
$[Rh(COD)_2]BF_4$ in dichloromethane at room temperature. Catalysts **A** and **B** were used in the asymmetric hydrogenation of methyl acetamidocinnamate under various conditions, and the results are summarised in Table 1. In protic solvents such as methanol and ethanol (entries 1 and 2) both catalysts gave satisfactory enantioselectivities. Further improvement was attained on using dichloromethane as the reaction solvent (entry 4). Excellent enantioselectivities were observed at lower temperatures (entries 5 and 6). A ten-fold reduction in the amount of the catalyst did not affect the stereoselectivity of the reaction (entry 4 versus entry 7) although the time required for complete conversion had to be extended. It is worth noting that for a given set of conditions catalyst **B** always showed better enantioselectivity over catalyst **A**. Thus, the incorporation of bis(3,5-dimethylphenyl)phosphinyl groups in **3** and **4** outperformed their parent ligands by a substantial margin (entry 4).

The general applicability of catalysts **A** and **B** in the hydrogenation of other (*Z*)-2-acetamido-3-aryl acrylic esters and acids was also examined. The reactions were carried out at room temperature in 10 min with a substrate concentration of 0.25 M in dichloromethane under 50 psi H_2 pressure, and the results are shown in Table 2. It was discovered that electron-donating substituents had no influence on the enantioselectivity (entries 2 and 3 versus 1) whilst the catalysts were slightly less effective when the substrates contained electron-withdrawing groups at the *para*-position (entries 4–6). The sterically more hindered *ortho*-substituted substrate (entry 7) and a heteroaromatic substrate (entry 8) could also be hydrogenated with comparable enantioselectivities. Unsubstituted acetamidoacrylic ester showed the best result (entry 9); however, the corresponding acid gave somewhat lower enantioselectivity. In all cases, catalyst **B** was again more effective than catalyst **A**, giving further credence to the beneficial effect of the 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl backbone. In addition, catalyst **B** was also found to exceed the performance of its parent ligand (entries 3, 5 and 7–9).

3. Conclusion

In summary, we have demonstrated that by simultaneously modifying the phosphinyl and binaphthalene moieties of the parent BINAPO ligand, it is possible to

Table 1. The enantioselective hydrogenation of methyl acetamidocinnamate using catalysts **A** and **B**[a]



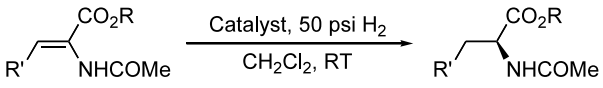
Entry	Solvent	Substrate/cat.	Temp. (°C)	ee% with catalyst **A**	ee% with catalyst **B**
1	Methanol	500	rt	83	89
2	Ethanol	500	rt	85	88
3	THF	500	rt	87	89
4	CH_2Cl_2	500	rt	92 (64)[b]	94 (84)[b]
5	CH_2Cl_2	500	0	94	96
6	CH_2Cl_2	500	−25	94	97
7[c]	CH_2Cl_2	5000	rt	92	94

[a] All reactions were performed at a substrate concentration of 0.25 M and under a hydrogen pressure of 50 psi and were completed within 10 min unless otherwise stated. Over >99% conversion were noted in all cases. Enantioselectivities and conversions were determined by GC with a CHROMPACK Chirasil-L-Val (25 m×0.25 mm) column. The *S*-product was obtained in all instances.

[b] Data in parentheses were obtained using corresponding catalysts with BINAPO and H_8-BINAPO ligands, respectively, under otherwise identical conditions.

[c] Quantitative yield was obtained within 30 min.

Table 2. The rhodium-catalysed enantioselective hydrogenation of dehydroamino acid derivatives using Xyl-BINAPO and Xyl-H_8-BINAPO as ligands[a]



Entry	Substrate	Catalyst **A**, ee%	Catalyst **B**, ee%[b]	Product configuration
1	R = Me, R′ = Ph	92	94	*S*
2	R = Me, R′ = 4-MeO-Ph	91	94	*S*
3	R = Me, R′ = 4-Me-Ph	92	94 (84)	*S*
4	R = Me, R′ = 4-AcO-Ph	90	93	*S*
5	R = Me, R′ = 4-Cl-Ph	91	93 (81)	*S*
6	R = Me, R′ = 4-NO_2-Ph	89	91	*S*
7	R = Me, R′ = 2-Cl-Ph	90	93 (85)	*S*
8	R = Me, R′ = 2-furanyl	89	92 (64)	*S*
9[d]	R = Me, R′ = H	94	97 (81[c])	*S*
10[e]	R = H, R′ = H	86	90	*S*

[a] Quantitative conversion was obtained within 10 min at ambient temperature in CH_2Cl_2. Sub./cat. = 500, [sub.] = 0.25 M. The enantioselectivities and conversions were determined by GC with a CHROMPACK Chirasil-L-Val (25 m×0.25 mm) column. These conditions were applied in all cases unless otherwise stated.

[b] Data in parentheses were obtained using corresponding catalysts with H_8-BINAPO ligand.

[c] Only 49% conversion.

[d] The ee value and conversion were determined by GC with a CP-Chirasil-Dex (25 m×0.25 mm) column.

[e] Methanol was used as solvent for the reaction. The determination of ee and conversion was accomplished by transforming the acid product to the corresponding methyl ester followed by GC analysis with a CP-Chirasil-Dex CB (25 m×0.25 mm) column.

improve greatly the enantioselective hydrogenation of (*Z*)-acetamido-3-substituted acrylic esters. Continuing efforts will be focused on the use of these new ligands in reactions where BINAPO failed to work effectively as a catalyst.

4. Experimental

4.1. General

All experiments were carried out under a nitrogen atmosphere using standard Schlenk techniques or in a glovebox. Flash column chromatography was performed on silica gel (Merck Kieselgel 60, particle size 0.032–0.063 mm). Hexane, toluene, tetrahydrofuran and diethyl ether were distilled from sodium or sodium benzophenone ketyl before use. Methanol and ethanol were distilled from magnesium/iodine. Dichloromethane was distilled from CaH_2. ^1H, ^{31}P and ^{13}C NMR were recorded on a Varian AS 500 at rt using $CDCl_3$ as solvent. Enantiomeric excesses were determined by gas chromatographic analyses conducted on a HP 4890A or HP 5890 series II system. Bis(3,5-dimethylphenyl)phosphine chloride was prepared according to a literature procedure.[4a]

4.2. (*S*)- and (*R*)-2,2′-Bis[bis(3,5-dimethylphenyl)-phosphinoyl]-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl, (*S*)-4 and (*R*)-4

Bis(3,5-dimethylphenyl)phosphine chloride (691 mg, 2.5 mmol) was added over a period of 20 min to a cooled solution of dry triethylamine (0.8 ml, 6.1 mmol), (*S*)-2,2′-dihydroxy-5,5′-6,6′7,7′,8,8′-octahydro-1,1′-binaphthyl (292 mg, 1.0 mmol) and 4-*N*,*N*′-dimethylaminopyridine (15 mg, 0.1 mmol) in dichloromethane (30 ml) at 0°C. The reaction mixture was vigorously stirred for 3 h at the same temperature before removing the solvent under reduced pressure. The residue was dissolved in toluene (15 ml) and purified by flash column chromatography (silica gel, eluent: toluene) to afford the title compound as white solids (645 mg, 85%): decomp. temp. 213°C; $[\alpha]_D^{20}$ −66.2 (*c* 1.25, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.52–1.68 (m, 8H), 2.21 (s, 12H), 2.19 (s, 12H), 2.14–2.23 (m, 2H), 2.38–2.42 (m, 2H), 2.60–2.64 (m, 2H), 2.69–2.75 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 21.39, 21.48, 23.22, 23.30, 27.80, 29.76, 115.28, 115.41, 127.36, 127.54, 127.65, 127.84, 129.09, 130.85, 131.01, 131.33, 137.03, 137.59, 142.11, 142.26. ^{31}P NMR ($CDCl_3$): δ 109.7. Anal. calcd for $C_{52}H_{56}O_2P_2$: C, 80.59; H, 7.28; O, 4.13; P, 7.99. Found: C, 80.67; H, 7.22, O, 4.20; P, 7.89%.

Spectral data of (*R*)-**4** were identical to those of the (*S*)-isomer but the former decomposes at 214°C and shows an optical rotation of $[\alpha]_D^{20}$ +66.4 (*c* 1.38, $CHCl_3$).[9]

4.3. Typical procedures for the Rh-catalysed asymmetric hydrogenation of amidoacrylic acids and esters

In a glovebox, $[Rh(COD)_2]BF_4$ (0.01 mmol), the phosphinite ligand (0.01 mmol) and dried CH_2Cl_2 (1 ml) were placed in a 4 ml glass bottle and stirred at rt for 1 h to prepare a stock solution of the catalyst. In a typical experiment, the catalyst solution (10 μl, 0.0001 mmol) was added in a 50 ml autoclave, which was charged with the substrate (0.05 mmol) and solvent (190 μl). The autoclave was purged with hydrogen gas

three times before finally being pressurised with 50 psi H_2. The mixture was stirred at rt for 10 min after which the H_2 was released. The enantiomeric excesses and conversion were determined by GC analysis. The hydrogenation product of acetamidoacrylic acid was converted to its methyl ester before GC analysis with a capillary chiral column (CHROMPACK CP Chirasil-DEX CB, 25 m×0.25 mm column or CHROMPACK Chirasil-L-Val, 25 m×0.25 mm column).

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