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A Highly Effective Phosphinite Ligand Derived from D-Mannitol For Rh-Catalyzed Asymmetric Hydrogenation

Yixin Chen, Xingshu Li, Siu-kuen Tong, Michael C. K. Choi, Albert S. C. Chan*

Union Laboratory of Asymmetric Synthesis and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong, China

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Abstract: *A novel chiral phosphinite 1,2,5,6-di-isopropylidene-3,4-bis(diphenylphosphino)-D-mannitol was prepared and its rhodium complex was found to be an effective catalyst for the asymmetric hydrogenation of amidoacrylic acid and its derivatives with product ee's ranging from 90% to 97%.* © 1999 Elsevier Science Ltd. All rights reserved.

Key words: rhodium, asymmetric hydrogenation, D-mannitol, phosphinite, α-amidoacrylic acid

Chiral amino acids are important for the pharmaceutical industry both as nutritional supplements and as synthetic intermediates. A convenient method for the synthesis of these compounds is through the homogeneous catalytic asymmetric hydrogenation of prochiral amidoacrylic acids. Rhodium catalysts containing chiral phosphine ligands have proved to be highly effective for this type of reaction.[1] In contrast, similar catalysts containing common chiral phosphinite ligands have been found to be less effective. In recent years, much effort has been made in the preparation of chiral phosphine and phosphinite ligands from natural chiral pools. Selke *et al* [2] reported the use of a series of chiral phosphinite ligands derived from glucose for the rhodium-catalyzed asymmetric hydrogenation of dehydroamino acid derivatives to give good to excellent results. Further improvements of this type of ligand were achieved by RajanBabu et al.[3] The use of carbohydrates and derivatives as starting materials for the synthesis of chiral ligands has several advantages: 1) the raw materials are of high optical purity and are readily available; 2) the multifunctional property makes it possible to design various structures through a series of modifications. In the course of developing new chiral phosphinite ligands from inexpensive chiral pools, we have synthesized a new ligand, 1,2,5,6-di-*iso*-propylidene-3, 4-bis(diphenylphosphino)-*D*-mannitol [abbreviated as *D*-DIMOP (**1**)] and found it to be highly effective for the Rh-catalyzed asymmetric hydrogenation of α-amidoacrylic acid and its derivatives.

In a previous study we found that rhodium complexes bearing (*R*)- or (*S*)-spiro phosphinite ligands to be highly effective in the enantioselective hydrogenation of a variety of α,β-unsaturated α-amido carboxylic acids and their esters.[4] Excellent enantioselectivity and high catalytic activity were observed in the hydrogenation of α-amidoacrylic acid and its derivatives. The high enantioselectivity was attributed to the

* Corresponding author. Email: bcachan@polyu.edu.hk

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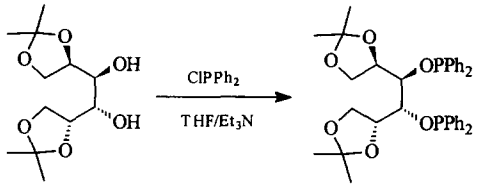
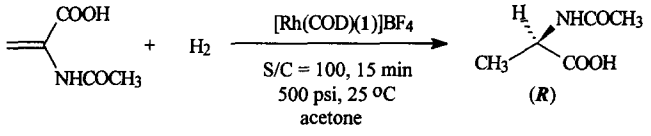
rigidity of the spirocyclic backbone of the phosphinite ligand. These results pointed to the importance of increased rigidity of the chiral backbones in the design of new ligands.

In this paper, we report the synthesis of DIMOP (**1**) and the use of it in the hydrogenation of amidoacrylic acid derivatives. DIMOP was prepared through the reaction of 1,2,5,6-di-*iso*propylidene-*D*-mannitol[5] with 2 equivalents of chlorodiphenyl phosphine in dry THF in the presence of triethylamine.[6] The bulky ketal groups on the chiral backbone of DIMOP significantly increase the rigidity of the phosphinite ligand in its transition-metal complexes. This effect was found to give positive influence on the enantioselectivity of the catalyst containing this ligand.



DIMOP (1)

High enantioselectivities were indeed found in the asymmetric hydrogenation of 2-acetamidoacrylic acid catalyzed by the cationic rhodium complex of DIMOP. When the reaction was carried out at ambient temperature and under 500 psi of hydrogen pressure for 15 minutes, a quantitative yield of the hydrogenation product with 96.7 % e.e. was obtained.



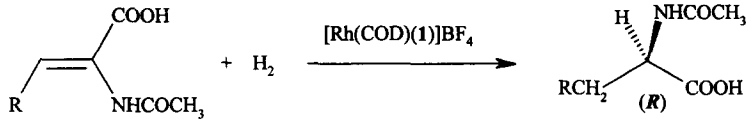
96.7% e.e.
100% conversion

A variety of 3-substituted (*Z*)-2-acetamidoacrylic acids were hydrogenated with the Rh(DIMOP)$^+$ catalyst and in all cases the desired products were found to have e.e.'s over 90%. More detailed data are summarized in Table 1. It is of interest to note that in contrast to the chiral phosphine rhodium-catalyzed asymmetric hydrogenation of prochiral amidoacrylic acids which gave lower product e.e.'s at lower reaction temperatures and under higher hydrogen pressure, higher e.e.'s were obtained for the Rh(DIMOP) system at lower temperature and higher H_2 pressure.

High enantioselectivity was also observed for the catalytic hydrogenation of (*Z*)-2-acetamidocinnamic acid methyl ester and its analogs catalyzed by Rh(DIMOP)$^+$. The detailed experimental results are listed in Table 2.

The effect of solvents on the enantioselectivity of the reaction was also significant. Typical results for the Rh(DIMOP)-catalyzed hydrogenation of methyl (*Z*)-2-acetamidocinnamate in different solvents are summarized in Table 3.

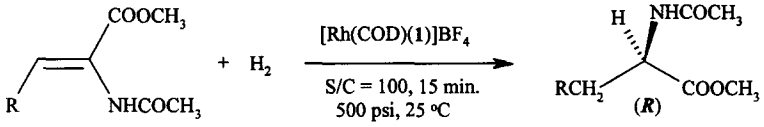
Table 1. Rh-(1) Catalyzed Asymmetric Hydrogenation of (*Z*)-2-Acetamidocinnamic Acid and Its Analogs[a]



Entry	Substrate (R)	PH_2 (psi)	Temp (°C)	e. e. %[b]	Config.
1	Ph	10-20	25	90.1	*R*
2	Ph	100	25	92.8	*R*
3	Ph	500	25	94.4	*R*
4	Ph	500	-15	97.1	*R*
5	4-Cl-Ph	500	25	93.3	*R*
6	4-Cl-Ph	500	0-5	94.6	*R*
7	4-Cl-Ph	500	-15	96.3	*R*
8	2-Cl-Ph	500	25	92.3	*R*
9	3-Cl-Ph	500	25	90.3	*R*
10	2-MeO-Ph	500	25	93.2	*R*
11	3,4-(OCH_2O)-Ph	500	25	94.2	*R*

[a]Reaction conditions: reaction time=15-60 min; substrate/catalyst = 100 (mol : mol); solvent: acetone; 100% conversion was observed in all cases. [b]The e. e. values were determined by GLC using a Chrompack Chirasil-L-Val column after the products were converted to the corresponding methyl esters.

Table 2. Rh-(1) Catalyzed Asymmetric Hydrogenation of (*Z*)-2-Acetamidocinnamic Acid Methyl Ester and Its Analogs[a]



Entry	Substrate (R)	e. e. %[b]	Configuration
1	Ph	91.6	*R*
2	4-HO-Ph	91.5	*R*
3	4-MeO-Ph	91.4	*R*
4	4-Me-Ph	90.6	*R*
5	3-MeO-4-HO-Ph	90.2	*R*
6	3, 4-OCH_2O-Ph	93.2	*R*
7	4-Cl-Ph	91.3	*R*
8	4-Br-Ph	91.2	*R*
9	4-F-Ph	91.2	*R*
10	4-NO_2-Ph	90.5	*R*

[a]Reaction conditions: 500 psi of H_2 pressure; reaction time =15 min.; substrate : catalyst = 100 (mol : mol); acetone solvent; 100 % conversion was observed in all reactions. [b]The *e.* e. values were determined by GLC with a Chrompack Chirasil-L-Val column.

Table 3. The Effect of Solvent on the Hydrogenation of Methyl (*Z*)-2-Acetamidocinnamate Catalyzed by Rh(DIMOP)$^{+a}$

Entry	Solvent	e.e.(%)[b]	Configuration
1	Acetone	91.6	*R*
2	Methanol	84	*R*
3	Isopropanol	89.4	*R*
4	THF	86.3	*R*
5	Dichloromethane	86.2	*R*
6	Benzene	82.9	*R*

[a]Reaction condition: 500psi H_2 pressure; reaction time= 15 min.; substrate: catalyst = 100 (mol:mol); room temperature; 100% conversion was observed in all reactions. [b]The e.e. values were determined by GLC with a Chrompack Chirasil-L-Val column.

The high enantioselectivity of the Rh(DIMOP) catalyst system in the asymmetric hydrogenation of amidocinnamic acids was relatively independent of the substituents on the phenyl ring of the substrate. This general effectiveness of the catalyst offers excellent opportunities for the preparation of a variety of chiral amino acids with good ee's.

In conclusion, we have developed a chiral phosphinite ligand from the low cost raw material (*D*)-mannitol. The rhodium catalyst containing this ligand was highly effective in the asymmetric hydrogenation of a variety of prochiral enamides.

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6. **Preparation of 1,2,5,6-di-isopropylidene-3,4-bis(diphenylphosphino)-*D*-mannitol (1):** 1,2,5,6-di-isopropylidene-*D*-mannitol (2.62g, 0.01 mol), 4-*N,N*-dimethylaminopyridine (0.30g, 0.002 mol) and triethylamine (2.64 g, ,0.026 mol) in THF (30 ml) were charged to a 100 mL Schlenk flask under nitrogen atmosphere. The flask was cooled in an ice water bath. A solution of chlorodiphenylphosphine (4.7 ml, 0.026 mol) in THF (10 mL) was added dropwise to the above solution over a period of 4 hours. The ice water bath was removed and the mixture was stirred at room temperature for 8 hours. The solvent was removed in vacuo and 30 mL of anhydrous ether was added to dissolve the residue. The mixture was filtered through basic Al_2O_3 (10 g) under nitrogen atmosphere, and the filtrate was evaporated in vacuo to afford **1** as a colorless solid (5.46 g, 87% yield). ^{1}H NMR (400MHz, $CDCl_3$) δ: 1.13(s, 6H), 1.41(s, 6H), 3.59-3.3.68(m, 4H), 3.80-4.03(m, 4H), 7.22-7.88 (m, 20H). ^{31}P NMR (162 MHz, CD_3Cl) δ: 124.1 ppm. ^{13}C NMR (400 MHz, CD_3Cl) δ: 142.75 (d, JRh-C=16.9 Hz), 142.6 (d, JRh-C=16.2Hz), 130.51, 130.29, 130.05, 129.31, 129.24, 128.92, 128.40, 128.32, 128.24, 128.17, 109.32, 81.23 (d, JRh-C=18.2Hz), 72.67, 67.70, 26.60, 22.42; HRMS calcd for $C_{36}H_{40}O_6P_2$ (M^+) 630.2300, found 630.2264.