Highly Enantioselective Hydrogenation of Itaconic Acid Derivatives with a Chiral Bisphospholane-Rh(I) Catalyst

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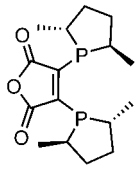
Received: March 12, 2004; Accepted: August 12, 2004

Abstract: The new – commercially in multi-kg quantities available – chiral bisphospholane ligand, cat*A*-*S*ium® M, has been successfully used in the Rh(I)-catalysed enantioselective hydrogenation of itaconic acid derivatives. Chiral ß-substituted succinic acid derivatives were produced in good to excellent enantioselectivities. Turnover frequencies by up to 40,000 h^{-1} have been achieved.

Keywords: asymmetric catalysis; chiral bisphospholanes; enantioselective hydrogenation; homogeneous catalysis; P ligands; rhodium

The increasing use of chiral building blocks in pharmaceuticals, agrochemicals, flavours, and fragrances has rendered the enantioselective synthesis of chiral compounds on an industrial scale an important topic.[1] Since the seminal work in 1968 by Knowles[2a] and Horner[2b] on the application of chiral phosphane ligands for the Rh-catalysed enantioselective reduction and the first industrial application to the synthesis of L-DOPA,[3] literally more than hundreds of chiral trivalent phosphorus-containing ligands have been synthesised and tested in the metal-catalysed homogeneous hydrogenation of functionalised and non-functionalised olefins, ketones, imines and other prochiral substrates.[4] Diphosphanes like DIOP,[5] DIPAMP,[6] BINAP,[7] JOSIPHOS[8] and DUPHOS[9] representing so-called privileged ligands have found several applications in the industrial production of chiral intermediates.[10] In particular, the chiral bisphospholane DUPHOS and its derivatives turned out to be one of the most powerful ligands, apparently due to the proximity of the chiral information to the catalytically active centre in relevant Rh complexes and the high basicity of the ligating phosphorus atoms. Unfortunately, from the synthetic point of view, the synthesis of DUPHOS seems to be rather expensive, due to the use of precious benzene-1,2-diphosphane as starting material.

Recently, we have developed a facile access to the new chiral phospholane ligand **1**, called cat*A*Sium® M.[11,12] First applications in the enantioselective preparation of chiral β-amino acid derivatives showed the high catalytic potential of Rh complexes based on cat*A*Sium® M.



1 catASium® M

Interestingly, in several cases the Rh catalyst of the new phospholane showed superior catalytic properties in comparison to a related DUPHOS complex. Prompted by these promising results we envisaged the hydrogenation of other substrates. We were particularly interested in the preparation of enantiomerically pure β-substituted succinic acids by hydrogenation of corresponding itaconic acid derivatives. The products are chiral bifunctional C_5-building blocks which are important intermediates for the preparation of natural products and pharmaceuticals.[13] Here we present our results on the enantioselective synthesis of succinic acid derivatives by employment of Rh complexes of cat*A*Sium® M.

First studies on the hydrogenation of dimethyl itaconate (**2a**) were performed under isobaric conditions at a hydrogen pressure of 4 bar (Table 1). In order to elucidate the effect of the type of the catalyst preparation on the hydrogenation we employed the *in situ* prepared precatalyst and the isolated precatalyst, respectively. When an *in situ* generated precatalyst was used, the chiral ligand **1** and $Rh(COD)_2BF_4$ were stirred at room temperature for 20 minutes before the addition of the substrate occurred. In the subsequent hydrogenation dimethyl itaconate was reduced in methanol in 96% ee

 DOI: 10.1002/adsc.200404080

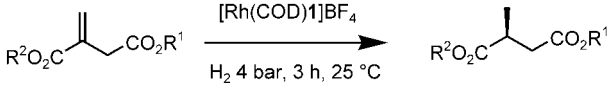
(entry 1). This value could be improved to 98% ee when the reaction was carried out in dichloromethane as solvent (entry 2). The enantioselectivity of our catalyst proved to be similar to that achieved with an Me-DUPHOS catalyst, which gave in our hand 97% ee. A further improvement of the ee was achieved by using the isolated Rh precatalyst (99% ee, entry 3). In this case the isolated Rh complex was dissolved prior to the addition of the substrate. Finally under optimal reaction conditions dimethyl itaconate could be completely reduced at a TON 10,000 within fifteen minutes with an enantiomeric excess of 99% (entry 4). In order to achieve such high turnover frequencies it was necessary to use a higher pressure (8 bar). It is worthy of mention that the elevated pressure did not affect the ee.

Not only could dimethyl itaconate (**2a**) be reduced in excellent enantioselectivities, but also itaconic acid (**2b**) was hydrogenated with 97% ee. Addition of a base slightly increased the enantioselectivity to 98% (entry 6). Another interesting substrate is the mono-ester **2c**. The product of the hydrogenation, (*R*)-2-methylsuccinic acid 4-methyl ester, represents a valuable building block because of the different reactivities of both carboxylic groups.[13] High enantioselectivities were obtained in the hydrogenation of this substrate both in methanol and dichloromethane (entries 7–9). Using the same precatalyst and by modifying the reaction conditions, it was found that our cat*A*Sium® M in dichloromethane at S/C 1,000 and at an initial pressure of 8 bar catalysed the reduction of substrates **2** in 98% ee. It is worthy of note that under the same reaction conditions in a parallel experiment Me-DUPHOS only gave 10% ee.[14]

For the reduction of β-substituted itaconic acid derivatives only a few systems are known which provide satisfactory enantioselectivities.[15] Substrates **2d**,**e** were easily prepared from dimethyl succinate and benzaldehyde and isobutyraldehyde, respectively, *via* Stobbe condensation.[16] The obtained *E*/*Z*-isomeric mixtures of the substrates were subjected to the hydrogenation procedure. Results are listed in Table 2. 2-Benzylidenesuccinic acid 1-methyl ester (**2d**) was hydrogenated with an *in situ* generated precatalyst of cat*A*Sium® M in methanol with 86% ee (entry 1). When dichloromethane was used as solvent the enantioselectivity could be improved to 98% (entry 2). Similar results were noted on application of substrate **2e**. In methanol good enantioselectivities were obtained (91% ee, entry 3). By application of acetone as solvent still higher enantioselectivities could be achieved (95% ee, entry 4). When the precatalyst was isolated prior to the hydrogenation, dichloromethane was found to be the solvent of choice (94% ee, entry 5). The presence of one equivalent of an amine further increased the enantioselectivity to 96% (entry 6). In general enantioselectivities registered are comparable with those obtained with the related Rh-Me-DUPHOS catalyst which gave under the same reaction conditions in our hands 96% ee.

In conclusion, a rhodium(I) catalyst based on the new chiral bisphospholane ligand **1** (cat*A*Sium® M) repre-

Table 1. Hydrogenation of non-substituted itaconates **2a–c**.[a]



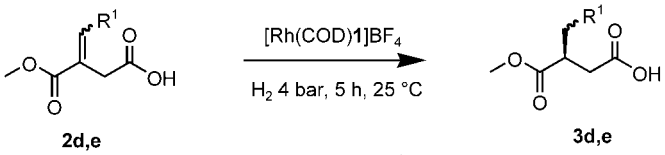
2a - c **3a - c**

2a: $R^1 = R^2 = Me$
2b: $R^1 = R^2 = H$
2c: $R^1 = Me$; $R^2 = H$

Entry	Substrate	Type of precatalyst	Solvent	TON	ee [%]
1	**2a**	prepared *in situ*	MeOH	400	96
2	**2a**	prepared *in situ*	CH_2Cl_2	500	98
3	**2a**	Isolated	MeOH	500	99
4[b]	**2a**	Isolated	CH_2Cl_2[c]	10,000[d]	99
5	**2b**	Isolated	MeOH	500	97
6	**2b**[e]	Isolated	MeOH	500	98
7	**2c**	Isolated	MeOH	400	98
8[b]	**2c**	Isolated	CH_2Cl_2	1,000	98
9	**2c**	Isolated	CH_2Cl_2	4,000[f]	99

[a] Unless indicated otherwise, the substrate concentration was 0.5 M. Unless indicated otherwise, all the reactions were run at 4 bar hydrogen for 3 h at 25 °C.
[b] The experiment was performed at 8 bar initial hydrogen pressure.
[c] The substrate concentration was 1 M.
[d] An average TOF of 40,000 h^{-1} was calculated.
[e] One equivalent of *i*-Pr_2NEt was added.
[f] TOF = 8,000 h^{-1}.

Table 2. Hydrogenation of β-substituted itaconic acid derivatives **2d, e**.[a]



2d,e **3d,e**

2d: R^1 = Ph **2e**: R^1 = *i*-Pr

Entry	Substrate	Type of precatalyst	Solvent	TON	ee [%]
1	**2d**	prepared *in situ*	MeOH	500	86
2	**2d**	prepared *in situ*	CH_2Cl_2	500	98
3	**2e**	prepared *in situ*	MeOH	192	91
4	**2e**	prepared *in situ*	Acetone	186	95
5	**2e**	Isolated	MeOH	196	90
6	**2e**	Isolated	CH_2Cl_2	196	94
7	**2e**[b]	Isolated	CH_2Cl_2	200	96

[a] Unless indicated otherwise, the substrate concentration was 0.5 M. Unless indicated otherwise, all the reactions were run at 4 bar hydrogen for 5 h at 25 °C.
[b] One equivalent of *i*-Pr_2NEt was added.

sents one of the most effective and enantioselective catalysts for the hydrogenation of non-substituted and β-substituted itaconic acid derivatives known up to now. The reported results show that our new ligand cat*A*Sium® M (**1**) displays higher performance in several reactions compared to the Me-DUPHOS ligand. The excellent enantioselectivities observed (up to 99%), the high catalytic activity (TOF up to 40,000 h^{-1}) and the availability of this ligand on a multi-kg scale makes it suitable for extensive industrial applications.[17] The synthesis of other members of this new ligand family as well as studies on synthetic applications in other reactions and their application in pilot plant processes are in progress.

Experimental Section

General Remarks

The precatalyst preparation and manipulation were performed in a glove-box under a dry argon atmosphere. Solvents were reagent grade and dried and distilled before use following standard procedures. $[Rh(COD)_2]BF_4$ was purchased from Heraeus and used as received. Dimethyl itaconate (**2a**) and itaconic acid (**2b**) were purchased (Aldrich) and used without further purification. The following compounds were synthesised according to literature procedures: **1**,[11] [Rh(COD)**1**]BF_4,[11], **2c**,[16] **2d**,**e** (used as a mixture of *Z* and *E* isomers).[15] Products **3b**,**c** were derivatised into their dimethyl esters prior to the reaction mixtures analyses. The absolute configuration of the products **3a – c** was assigned by analogy, through HPLC elution order with an enantiopure sample of dimethyl (*R*)-2-methylsuccinate. The absolute configuration of the products **3d**,**e** was assigned by comparisons of the rotation signs with literature data. Enantiomeric excesses were determined by HPLC: Chiralcel-OD column (250 mm × 4.6 mm) and detection by a diode array UV/Vis detector at 214 nm. For compounds **2a**,**b**,**e**: *n*-hexane/2-propanol 95/5; 1.25 mL/min; **2b, e** were converted into their dimethyl esters with TMSCl in methanol prior to the analysis. For compound **2c**: *n*-hexane/2-propanol, 90/10; 1.25 mL/min. For compound **2d**: *n*-hexane/2-propanol, 90/10; 1 mL/min; **2d** was converted into its dimethyl ester with TMSCl in methanol prior to the analysis. The values of turnover numbers and ee correspond to the average value of at least 2 experiments.

Typical Procedure for the Asymmetric Hydrogenations (Table 1, entry 4)

In an argon atmosphere, 0.1 mL of a 0.01 M solution of ligand **1** in methanol (0.001 mmol, 0.6 mg) was added to 0.1 mL of a 0.01 M solution of $Rh(COD)_2BF_4$ in methanol (0.001 mmol, 0.4 mg) and the resulting mixture was stirred at room temperature for 20 minutes. The precatalyst was transferred into a 50-mL Parr autoclave with a magnetic stirrer and then 10 mL of a 0.5 M solution of substrate **3a** in methanol (5 mmol, 0.8 g) were added. The autoclave was closed, purged with hydrogen and then pressurised with hydrogen to 4 bar. The reaction mixture was stirred at 25 °C for 3 h (the pressure was maintained around 4 bar by adding more hydrogen during the reaction). After 3 h the hydrogen was released and the reaction mixture was analysed by HPLC (0.5 mL was concentrated in vacuum; the residue was taken up into 0.5 mL *i*-PrOH and 0.5 mL *n*-hexane and filtered through a small plug of silica gel).

Typical Procedure for the Esterification of Hydrogenation Products with TMSCl

After evaporating the reaction solvents, the residues were taken up in 0.5 mL of a freshly prepared 2 M solution of trimethylsilyl chloride (TMSCl) in methanol and stirred at room temperature for 1 h. The solvents were evaporated (caution, evolution of HCl) and the residues were taken up in 0.5 mL of 2.5 M NaOH and extracted with *t*-butyl methyl ether (MTBE). The organic phase was separated and dried with Na_2SO_4. After the solvent switch to *i*-PrOH/*n*-hexane the reaction mixtures were analysed by HPLC.

Acknowledgements

We are grateful for the financial support provided by the BMBF and the Fonds der Chemische Industrie. We thank Dr. U. Dingerdissen and Prof. Dr. K.-H. Drauz for valuable discussions.

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