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Asymmetric Hydrogenation of Vinylphosphonic Acids and Esters with Chiral Ru(II) Catalysts

J.-C. Henry, D. Lavergne, V. Ratovelomanana-Vidal, J.-P. Genêt#

Laboratoire de Synthèse Sélective Organique et Produits Naturels, Associé au C.N.R.S, Ecole Nationale Supérieure de Chimie de Paris, 11 rue P. et M. Curie, 75231 Paris Cedex 05, France.

I. P. Beletskaya, T. M. Dolgina

Department of Chemistry, Moscow State University, 119899 Moscow, GSP-3, Russia

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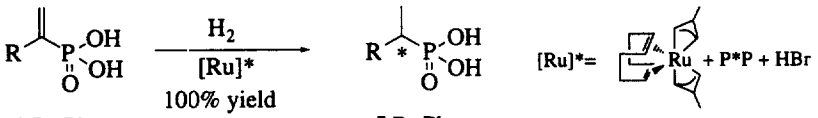
***Abstract**: The first asymmetric hydrogenation of vinylphosphonic acids and esters to the corresponding arylethylphosphonic acids and esters using chiral Ru(II) catalysts is reported with enantiomeric excesses up to 86%.*

The transformations of α,β-unsaturated carboxylic acids such as 2-arylpropenoic acids to chiral acids *via* enantioselective ruthenium-mediated hydrogenation is now of industrial importance for the production of non steroidal antiinflammatory drugs naproxen[1] and ibuprofen. Considering analog design, the use of phosphonic acid as analogs of the corresponding phosphates and carboxylates has stimulated significant interest in the search of new potent drugs of pharmaceutical interest.[2] It is well established that alkenylphosphonates are biologically active compounds[3] and important intermediates in the synthesis of antibiotics such as fosfomycin.[4] As an extension of our previous work[5], we report in this paper the ruthenium-catalyzed homogeneous hydrogenation of α,β-unsaturated phosphonic acids (scheme 1) and esters as analogues of the corresponding carboxylic acids.



1 R=Ph
2 R=*p*-Me-Ph
3 R=*p*-Cl-Ph
4 R=1-Napht

5 R=Ph
7 R=*p*-Me-Ph
8 R=*p*-Cl-Ph
9 R=1-Napht

P*P = BINAP, MeO-BIPHEP DuPHOS

scheme 1

Number of synthesis of alkenylphosphonic acids and esters have been reported.[6] The Pd-catalyzed hydrophosphorylation of alkynes has recently been described with high yields.[7] Heterogeneous hydrogenation of these compounds using Pd on activated carbon at 3.4 bars was described[2f,3b,8] as well as the chemoselective reduction of double bond of α,β-unsaturated phosphonates catalyzed by $[Pd(O_2PBu^t_2)(OPBu^t_2)(OHPBu^t_2)]$ in good yields.[9] To our knowledge, there is no report on the asymmetric homogeneous hydrogenation[10] of α,β-unsaturated phosphonates involving chiral transition metal catalysts such as chiral Ru(II)-catalysts. In preliminary studies, asymmetric hydrogenation was performed in methanol with complete conversion using the chiral catalyst (*S*)-$BinapRuBr_2$ prepared *in situ*[5d,e] and 1-phenylethenylphosphonic acid **1** or ester **6** as representative examples, in order to optimize experimental conditions (scheme 2).

#FAX : (33)1 44 07 10 62; E-mail : genet@ext.jussieu.fr

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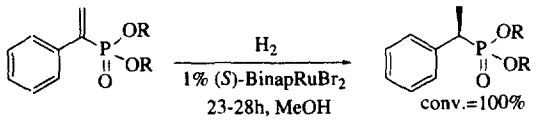
We noted that enantiomeric excesses were dependent on the temperature : better selectivities were reached when the reaction was carried out at 80°C, compared to room temperature, and this under 1 to 100 bars of hydrogen pressure (table 1). In the case of **1**, the reaction proceeded smoothly at atmospheric pressure and room temperature leading to (*R*)-1-phenylethylphosphonic acid **5** with 54% e.e. (entry 1). An improved enantiomeric excess of 68% was obtained at 80°C (entry 2). The best selectivity was observed at 80°C (entry 3, 73% e.e.) under 10 bars of hydrogen pressure while under 100 bars and 80°C, a decreased enantioselectivity (entry 4, 63% e.e.) was obtained. The phosphonate **6** did not undergo hydrogenation at low pressure and temperature but under 80 bars and 80°C (entry 5) to afford diethyl 1-phenylethylphosphonate ester **10** with 66% e.e.

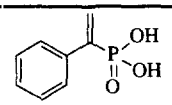
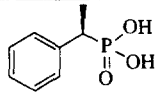
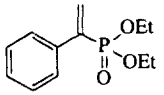
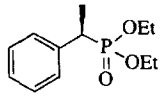


1 R=H
6 R=Et

5 R=H
10 R=Et

scheme 2

Table 1: Optimization of asymmetric hydrogenation with 1-phenylethenylphosphonic acid and ester

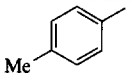
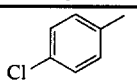
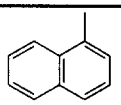
Entry	Substrate	Pressure (bars)	Temp. (°C)	Product	e.e. (%)
1		1	r.t.		54
2	**1**	1	80	**5**	68
3	**1**	10	80	**5**	73
4	**1**	100	80	**5**	63
5		80	80		66[a]
	6			**10**	

(a) E.e. was measured by GC analysis (Megadex 5 column)

Under these optimized conditions, we investigated the asymmetric hydrogenation of the 1-arylvinylphosphonic acids **1-4** under 10 bars and 80°C using various Ru(II)-catalysts[5e] bearing either BINAP or other phosphines as chiral ligands (table 2). 1-phenylethenylphosphonic acid **1** was hydrogenated to (*R*)-1-phenylethylphosphonic acid **5** using (*S*)-BINAP as ligand with 73% e.e. (entry 1). The absolute configuration (*R*) of compound **5** was assigned from the optical rotation value of the corresponding dimethylphosphonate $[\alpha]_D$=+4 (c 1.34, $CHCl_3$), obtained after treatment of **5** with diazomethane, by comparison with literature data[11] ($[\alpha]_{Dlit}$=+5.17(c 1.15, $CHCl_3$, e.e.>95%) for the (*R*)-enantiomer). The absolute configuration of **7** was assigned by comparison of the α value of the corresponding dimethylester $[\alpha]_D$=-7 (c 1.03, $CHCl_3$) with that of an authentic sample of the (*S*)-enantiomer, prepared according to Hanessian's procedure, $[\alpha]_D$=-5 (c 0.98, $CHCl_3$, e.e.=63%).[12] According to these results, a general sense of the hydrogenation was observed : the absolute configuration (*R*) of the atropoisomeric ligand afforded the (*S*)-enantiomer of the arylethylphosphonic

acids. Thus, we anticipated that the hydrogenation of phosphonic acids **3** and **4** carried out with the atropoisomeric ligand (*R*)-MeO-BIPHEP led to the (*S*)-configuration of **8** and **9**. When the hydrogenation was conducted with (*R,R*)-Me-DuPHOS, a poor e.e. was observed (entry 3, 21% e.e.). Similar enantiofacial discriminations were obtained for compounds **2** and **3** irrespective of the substitution of the phenyl ring (methyl or a chlorine group, entries 4, 5, 7 and 8) with selectivities ranging from 71 to 80%. Once again, (*R*)-MeO-BIPHEP gave better e.e. (entries 5 and 8, 78% and 80% e.e.) than (*S*)-BINAP (entries 4 and 7, 71% and 74% e.e.) while (*R,R*)-Me-DuPHOS led to very modest enantioselectivities (entries 6 and 9, 16% and 25% e.e.).

Table 2: Asymmetric hydrogenation of vinylphosphonic acids and esters with (P*P)$RuBr_2$.

Entry	Substrate (R=)	[Ru]* (P*P)	e.e. [a] (%)	Conf.
1		(*S*)-BINAP	73	(*R*)-**5**
2		(*R*)-MeO-BIPHEP	77	(*S*)-**5**
3	**1**	(*R,R*)-Me-DuPHOS	21	(*R*)-**5**
4		(*S*)-BINAP	71	(*R*)-**7**
5		(*R*)-MeO-BIPHEP	78	(*S*)-**7**
6	**2**	(*R,R*)-Me-DuPHOS	16	(*R*)-**7**
7		(*S*)-BINAP	74	(*R*)-**8**
8		(*R*)-MeO-BIPHEP	80	(*S*)-**8**
9	**3**	(*R,R*)-Me-DuPHOS	25	(*R*)-**8**
10		(*S*)-BINAP	73	(*R*)-**9**
11		(*R*)-MeO-BIPHEP	86	(*S*)-**9**
12		(*R,R*)-Me-DuPHOS	37	(*R*)-**9**
	4			

(a) The enantiomeric excesses of the phosphonic acids **5**, **7**, **8** and **9** were measured in ^{31}P NMR after treatment with (*1S,2S*)-(-)-*N,N'*-diphenylethylenediamine in $CDCl_3$ and catalytic amount of CD_3OD.

Finally, 1-(1-naphtyl)ethenylphosphonic acid **4** was totally reduced using (*R*)-MeO-BIPHEP under the above conditions with good enantioselectivity (entry 11, 86% e.e.) to the corresponding saturated 1-1-(naphtyl) ethylphosphonic acid (*S*)- **9**

In conclusion, enantioselective homogeneous ruthenium-mediated hydrogenation of α,β-unsaturated phosphonic acids and ester was achieved with good enantiofacial discrimination affording arylethylphosphonic acids, analogues of the antiinflammatory carboxylates.

Acknowledgments : We are grateful to Dr. R. Schmid (Hoffmann La Roche) for samples of (*R*) and (*S*)-MeO-Biphep = (*R*)-(+)-6,6'-dimethoxy-2,2'-bis(diphenylphosphino)-1,1'-biphenyl. We also thank financial support from grant INTAS-93-1482-ext.

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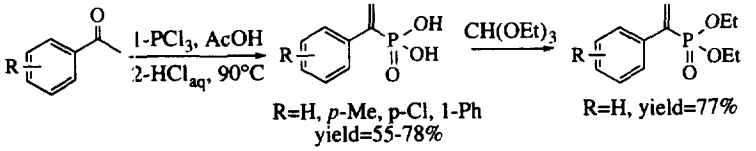

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12. The reaction was conducted as described below :