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Enantioselective hydrogenation of exocyclic α,β-unsaturated ketones Part II. Hydrogenation in the presence of (*S*)-proline

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Abstract

In the asymmetric synthesis of chiral compounds, the reduction of prochiral unsaturated reactants has a great importance. (*S*)-proline as a chiral auxiliary is used in the hydrogenations of exocyclic α,β-unsaturated ketones with palladium on carbon catalysts, producing the corresponding saturated ketones with an optical purity up to 20%. The influence of the parameters (solvents, additives) on the optical yield is also investigated. The highest enantioselectivity was obtained in ethyl acetate and acetonitrile (ee 20%), at atmospheric pressure and room temperature.

Keywords: Enantioselective hydrogenation; Exocyclic α,β-unsaturated; (*E*)-2-benzylidene-1-benzosuberone; (*S*)-proline; Palladium catalyst; Enantiomeric excess

1. Introduction

Reduction of prochiral unsaturated substrates is an important method for the synthesis of chiral compounds. There are several ways to prepare an optically active compound by reduction:

- use of a chiral reducing agent,
- hydrogenation with homogeneous chiral metal complex catalyst, or with the same anchored on a support material,
- diastereoselective reduction of optically active substrate, and
- hydrogenation with heterogeneous catalyst modified by chiral compounds.

The enantioselective heterogeneous hydrogenation of the C=C double bond of α,β-unsaturated acids and esters (particularly those bearing a nitrogen atom in α-position) has been extensively studied [1–3]; such a reaction for α,β-unsaturated ketones has been relatively well documented also, including mechanistic studies [4,5].

Reports about (*S*)-proline mediated enantioselective synthesis, for example the hydrogenation of isophorone [6] prompted us to use proline as a chiral auxiliary in other hydrogenations too.

This method differs from the modified catalyst systems, since the chiral agent is added in stoichiometric amount directly to the reaction mixture. It was proved that (*S*)-proline/isophorone interaction is a specific reversible chemical reaction [6].

Pd-on-carbon catalyst in presence of (*S*)-proline afforded dihydroisophorone in high (up to 60%)

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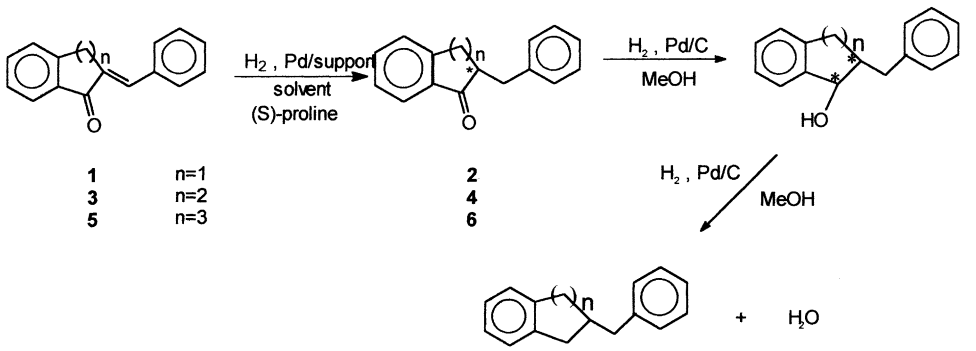


Scheme 1. The heterogeneous catalytic hydrogenation of (*E*)-2-benzylidene-1-indanone, (*E*)-2-benzylidene-1-tetralone and (*E*)-2-benzylidene-1-benzosuberone.

enantiomeric excess. An oxazolidinone intermediate was formed prior to the hydrogenation by condensation reaction of the (*S*)-proline and the unsaturated ketone. The optically active saturated ketone arose from the chemo- and diastrereoselective hydrogenation of the C=C double bond in the oxazolidinone [7].

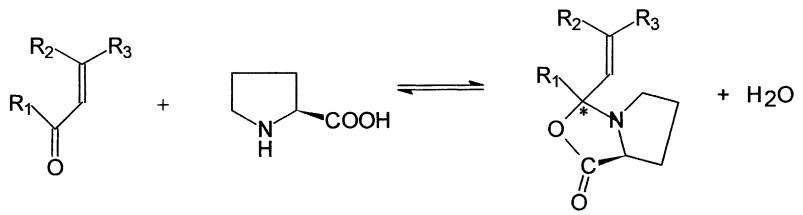
Using the same method ((*S*)-proline, Pd/C, in methanol) for exocyclic α,β-unsaturated ketones the chemoselectivity towards saturated ketones was not complete 90% or less and the ee was poor.

In this work, the heterogeneous catalytic hydrogenation of (*E*)-2-benzylidene-1-indanone (**1**) to 2-benzyl-1-indanone (**2**), (*E*)-2-benzylidene-1-tetralone (**3**) to 2-benzyl-1-tetralone (**4**) and (*E*)-2-benzylidene-1-benzosuberone (**5**) to 2-benzyl-1-benzosuberone (**6**) was investigated in order to find reaction conditions where one can obtain higher enantioselectivity (Scheme 1). The substrates can take up 3 mol hydrogen in consecutive reactions according to Scheme 1. Uptake of the first mole of hydrogen results in the saturation of the C=C double bond, the next one reduces C=O double bond and, finally, the hydroxyl group is hydrogenolyzed.

The zwitterionic form of proline gives an addition and/or condensation product with the α,β-unsaturated ketone for examples isophorone (Scheme 2).

In the case of the exocyclic α,β-unsaturated ketones, the equilibrium concentration of such condensation product is probably much smaller. In order to promote the reaction between the (*S*)-proline and the substrate, sodium methylate (NaOMe) was added to the reaction mixture. In the sodium salt, the reactivity of the (*S*)-proline grew. As a result the reduction became chemoselective and gave higher optical purity for the corresponding saturated ketone.

The hydrogenation of (*E*)-2-benzylidene-1-benzosuberone (**5**) in methanol in the presence of (*S*)-proline and NaOMe was carried out, at room temperature under atmospheric pressure; it resulted in 2-benzyl-1-benzosuberone (**6**) with 100% selectivity and 12% optical purity.



Scheme 2. The possible condensation reaction between (*S*)-proline and an α,β-unsaturated ketone.

2. Experimental

2.1. Materials

Compounds **1** and **3** were prepared according to the procedure described in [8], while **5** was synthesized as described in [9].

The catalyst was commercial product: 10% Pd/C (Selcat) [10] (Fine Chemicals Co., Budapest, Hungary); (*S*)-proline was purchased from Fluka; sodium methylate from Merck; acetic acid and pyridine, the solvents: methanol, acetonitrile, tetrahydrofurane, dichloromethane, toluene, isopropanol, morpholine, hexane, acetone, cyclohexane, dimethylformamide, ethyl acetate were supplied by Reanal, Budapest, Hungary.

The amino acids: L-phenylalanine, D-phenylglycine, L-asparagine, D-valine L-glutamic acid, L-aspartic acid, L-lysine, L-alanine, L-isoleucine, L-serine, L-threonine, L-tryptophan, L-arginine were also supplied by Reanal, Budapest, Hungary.

2.2. Hydrogenations

The hydrogenations were carried out in a conventional apparatus with magnetic stirrer at atmospheric pressure. The working-up procedure of the reaction mixtures was the catalyst filtration and the removal of the solvent in vacuum. The residue was dissolved in dichloromethane and extracted with 5% HCl and distilled water. The organic phase was separated and dried over Na_2SO_4. After filtration, the solvent was removed in vacuum.

The product was analyzed by HPLC, from these data conversion, selectivity and enantioselectivity values were calculated.

2.3. Analysis

The determination of the absolute configuration was based on the literature data [11,12]. Supposing the same absolute conformation (same sign of the O–C–C_{Ar}–C_8 torsion angle), the negative sign of the $n\pi^*$ band at 319.6 nm ($[\theta] = 1221$, $c = 2.34$ mmol/l, in EtOH) suggest (*R*) absolute configuration of the chiral center.

The NMR spectra were recorded on a Bruker DRX500 spectrometer in $CDCl_3$ and CD_3CN.

Circular dichroism (CD) spectra were recorded on a Jobin Yvon Dichograph Mark VI.

Optical rotation data were measured with Perkin-Elmer 241 automatic polarimeter ($c = 1$ MeOH).

The HPLC analyses were carried out on a Chiracel OJ column (0.46 cm × 25 cm). The column contains silica-gel as packing material coated with a cellulose derivative. The eluent was hexan/2-propanol 90:10 (v/v), the flow rate was 1.0 ml/min. The UV absorbance was measured at 249 nm.

Enantiomeric excesses (%) were calculated according to the following equation:

$$\text{ee} = \frac{[\text{A}] - [\text{B}]}{[\text{A}] + [\text{B}]} \times 100$$

where [A] is the concentration of major enantiomer and [B] the concentration of minor enantiomer.

3. Results and discussion

3.1. Effect of additives

Giving the free amino acid, (*S*)-proline to the reaction mixture the selectivity of the hydrogenation of **5** was about 90% and the enantioselectivity was up to 10% in methanol (Table 1).

In these reactions, the effect of NaOMe/substrate ratio and the (*S*)-proline/substrate ratio were determined. The (*S*)-proline/substrate ratio, 1 mol/mol and the NaOMe/substrate ratio, 1 mol/mol gave the best enantiomeric excess. Not only the enantiomeric excess increased above 10%, but the initial reaction rates became higher also.

The effect of different basic and acidic additives such as NaOMe, pyridine and acetic acid on the enantioselectivity is shown in Fig. 1. Neither the basic pyridine and nor acetic acid produced the favorable effect of NaOMe.

3.2. Effect of amino acids

In the presence of other amino acids the selectivity of the hydrogenation of **5** was about 100% and the enantioselectivity was up to 12% in methanol (Table 2). Without NaOMe the hydrogenation gave racemic product.

Table 1
The effect of different amount of NaOMe on the enantioselectivity in the hydrogenation of **5**[a]

(*S*)-proline/substrate (mol/mol)	NaOMe/substrate (mol/mol)	Reaction rate (ml H_2/g_{cat} min)	ee[b] (%)	Configuration
1	1	65	12.3	*R*
1	2	53	4.5	*R*
1	0.5	66	11.5	*R*
0.5	1	25	6.7	*R*
0.5	2	47	2.8	*R*

[a] Conditions: 0.5 g (*E*)-2-bezylidene-1-benzosuberon (substrate), 0.05 g Pd/C (Selcat), 20 ml methanol, atmospheric pressure and 25 °C.
[b] ee: enantiomeric excess.

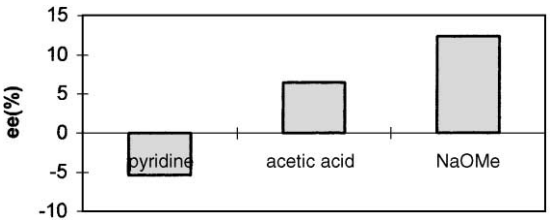


Fig. 1. Influence of additives on the enantioselectivity. Conditions: 0.5 g (*E*)-2-bezylidene-1-benzosuberon, 0.05 g Pd/C (Selcat), 20 ml methanol, 0.26 g (*S*)-proline, 1 mol equivalent additive, atmospheric pressure and 25 °C.

With other amino acids: L-glutamic acid, L-aspartic acid, L-lysine, L-alanine, L-isoleucine, L-serine, L-threonine, L-tryptophan, L-arginine, the optical purity was small (<6–7%).

Table 2
The influence of different amino acids on the enantioselectivity in the hydrogenation of **5**[a]

Amino acids	Reaction rate (ml H_2/g_{cat} min)	ee (%)	Configuration
L-Phenylalanine	104	12	*R*
D-Phenylglycine	67	8.4	*S*
L-Asparagine	102	8.0	*R*
D-Valine	95	8.3	*S*

[a] Conditions: 0.5 g substrate, 0.05 g Pd/C (Selcat), 20 ml methanol, 1 mol equivalent amino acid, 0.12 g NaOMe, atmospheric pressure and 25 °C.

3.3. Effect of solvents

The selectivity of the reaction, as well as the activity of the catalyst, can be influenced by using appropriate

Table 3
The influence of different solvents on the enantioselectivity in the hydrogenation of **5**[a]

Solvent	Reaction rate (ml H_2/g_{cat} min)	ee (%)	Configuration	Reaction rate (ml H_2/g_{cat} min)	ee (%)	Configuration
	Without additive			With NaOMe		
MeOH	64	10	*R*	88	12.3	*R*
MeCN	97	0	–	97	20.1	*R*
EtOAc	92	2.9	*R*	63	20.8	*R*
THF	28	3.4	*R*	30	1.5	*R*
DKM	18	4.4	*R*	0	0	–
Toluene	68	0	–	25	7.9	*R*
Morpholine	9	2.0	*R*	24	0	–
DMF	50	7.5	*R*	41	3.1	*R*
Hexane	–	–	–	98	7.0	*R*
Acetone	–	–	–	14	8.4	*R*
Cyclohexane	–	–	–	114	8.9	*R*
n-BuOH	–	–	–	17	3.9	*R*

[a] Conditions: 0.5 g (*E*)-2-bezylidene-1-benzosuberon, 0.05 g Pd/C (Selcat), 0.26 g (*S*)-proline, 0.12 g NaOMe, 20 ml solvent, atmospheric pressure and 25 °C.

Table 4
The effect of different solvents on the enantioselectivity in the hydrogenation of **1** and **3**[a]

Solvent	Substrates					
	1			**3**		
	Reaction rate (ml H_2/g_{cat} min)	ee of **2** (%)	Configuration	Reaction rate (ml H_2/g_{cat} min)	ee of **4** (%)	Configuration
MeOH	160	4.0	*R* [14]	100	8.6	*R* [12]
MeCN	37	13.8	*R*	51	10.0	*R*
EtOAc	20	9.0	*R*	15	6.2	*R*
Toluene	36	2.7	*R*	60	4.6	*R*

[a] Conditions: 0.5 g substrate, 0.05 g Pd/C (Selcat), 0.26 g (*S*)-proline, 0.12 g NaOMe, 20 ml solvent, atmospheric pressure and 25 °C.

solvents [13]. The results of the hydrogenations of the substrate (**5)** in different solvents, over palladium on carbon, are summarized in Table 3.

The conversion and the selectivity were 100% in all solvents. The initial rates were not changed with the polarity of the solvents. It is notable that in some solvents (EtOAc, THF, DKM, morpholine, DMF), without NaOMe, the product shows small optical activity (ee $<$ 5%). Significant enantioselectivity can be obtained only by using NaOMe. In two aprotic solvents (ethyl acetate and acetonitrile), the enantioselectivity was 20%, this can be attributed to the solubility of proline sodium. Among these conditions, the substrate (**1**) and (**3**) were hydrogenated too (Table 4).

Comparing the corresponding data of Tables 3 and 4, the enantiomeric excesses are lower in the hydrogenation of **1** and **3** than in that of **5**. Acetonitrile was the appropriate solvent in all reduction of **1**, **3** and **5**.

4. Conclusion

Exocyclic α,β-unsaturated ketones could be converted to the corresponding saturated ketones over palladium in different solvents with enantioselectivities up to 20%. The best solvent was acetonitrile (ee: (**2**) 13.8%, (**4**) 10.0% and (**6**) 20.0%). The highest optical purity (20%) was achieved in the reduction of (*E*)-2-benzylidene-1-benzosuberone, over palladium in the presence of stoichiometric amount of (*S*)-proline and NaOMe in ethyl acetate and acetonitrile. In this case, the strong basic additive (NaOMe) promoted the reaction between the substrate and the (*S*)-proline.

The enantioselectivity and the reaction rate were different for the five-, six- or seven-member saturated ring containing compounds under the same reaction conditions. These significant differences between the enantioselectivity values can be attributed to structural reasons as mentioned in [15].

The enantioselective hydrogenations of **1**, **3** and **5** with chiral modified catalyst is in progress.

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