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Dedicated to the memory of
Professor Mircea D. Banciu (1941–2005)

ENANTIOSELECTIVE HYDROGENATION OF EXOCYCLIC α,β-UNSATURATED KETONES. PART IV

HYDROGENATION WITH HOMOGENEOUS CATALYSTS

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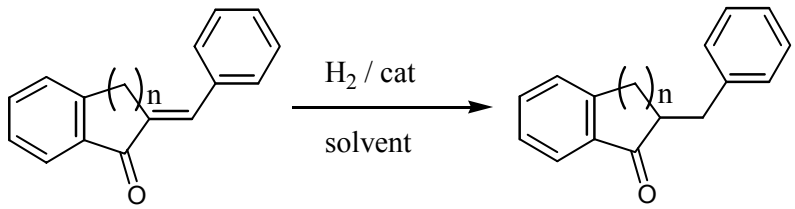
Homogeneous catalysts were used in the hydrogenation of exocyclic α,β-unsaturated ketones producing the corresponding saturated ketones up to 20% optical purity in methanol under hydrogen pressure. The influence of different parameters (solvent, nature of the metal, chiral ligand) on the optical yield was investigated.

Reduction of prochiral unsaturated substrates is an important method for the synthesis of chiral compounds. The enantioselective hydrogenation of exocyclic α,β-unsaturated ketones has been previously studied by some of us over heterogeneous catalysts using two approaches. In the first one, using a stoechiometric amount of proline, the highest enantioselectivity (up to 20%) in the hydrogenation of 2-benzyl-1-benzosuberone was achieved in acetonitrile in the presence of NaOMe.[1] A covalent bonding between proline and substrate was hypothesized, but in situ IR studies did not allow the detection of such a bonding whatever the reaction conditions.[2] In the second one, cinchonidine-modified palladium catalysts, known to reduce activated C=C double bonds with significant enantioselectivity were tested.[3] As far as exocyclic α,β-unsaturated ketones were concerned, the best ee (up to 54%) was achieved with Pd black in toluene in the presence of 5 wt % of modifier with respect to the catalyst.[4] Both approaches were applied to five-, six- and seven-membered ring substrates (scheme 1). The highest ee's were achieved for the seven-membered ring (2-benzylidene-1-benzosuberone). Molecular modeling showed that five- and six-members rings were nearly planar while the seven-membered ring was twisted.[5] Probably more specific interactions with the metallic surface occurred with that latter substrate.



1	n = 1	**4**
2	n = 2	**5**
3	n = 3	**6**

Scheme 1

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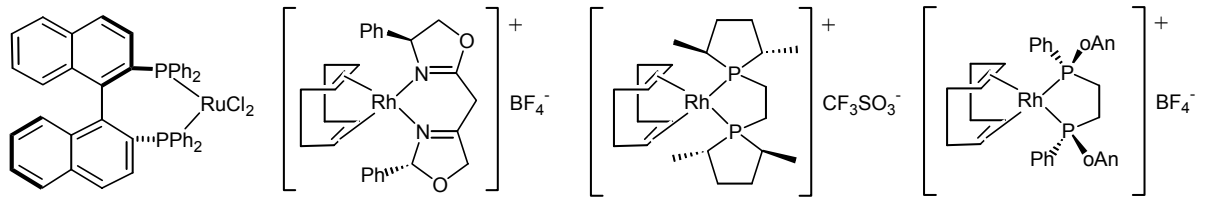

BinapRuCl$_2$ **7** BoxRhCOD **8** DuphosRhCOD **9** DipampRhCOD **10**

Scheme 2

Alternatively, enantioselective hydrogenation can be performed in the presence of homogeneous optically pure transition metal complexes. Tremendous success has been achieved with the use of chiral phosphine ligands in Rh- or Ru-catalyzed asymmetric hydrogenation reactions. Particularly, α,β-unsaturated ketone or ester have been hydrogenated over Ru-based catalysts with up to 95% enantioselectivity.[6]

In the present work, the homogeneously catalysed hydrogenation of (*E*)-2-benzylidene-1-indanone (**1**) to 2-benzyl-1-indanone (**4**), (*E*)-2-benzylidene-1-tetralone (**2**) to 2-benzyl-1-tetralone (**5**) and (*E*)-2-benzylidene-1-benzosuberone (**3**) to 2-benzyl-1-benzosuberone (**6**) was investigated in order to compare with the heterogeneous catalysts (Scheme 1).

(S)-(-)-BinapRuCl$_2$ **7** catalyst is known to be an efficient catalyst for asymmetric hydrogenation of α,β-unsaturated ketones.[6] We investigated the reaction conditions (solvent, pressure and temperature) in the hydrogenation of substrates **1-3** using this commercially available complex (Table 1).

Table 1

Influence of the reaction conditions in the presence of catalyst (S)-(-)-BinapRuCl$_2$ **7** on the enantioselectivity in the hydrogenation of **1-3**.

Substrate	Solvent	Pression (bar)	Temperature (°C)	Time (h)	Conv (%)	ee (%) (***R***)
3	MeOH	10	RT	72	3	nd
	MeOH	50	RT	72	15	15
	MeOH	50	50	72	82	2
	EtOH	50	RT	48	65	14
2	MeOH	50	RT	72	100	14
	MeOH	50	50	72	100	7
	CH_2Cl_2	50	RT	12	0	nd
	EtOAc	50	RT	17	0	nd
1	MeOH	50	RT	14	79	rac.

Conditions: 50 mg substrate, 2 mg catalyst (1 mol%), 10 ml solvent. nd: not determined; rac: racemic.

In the presence of 1 mol% complex, whatever the reaction conditions, only the hydrogenation of the C=C double bond was observed, even under high pressure and long reaction time: a complete chemoselectivity was achieved while in the presence of heterogeneous catalysts, C=O was subsequently hydrogenated.[5] Under 10 bar of hydrogen, the reaction rate was very low and the conversion reached only 3% after 3 days. Reasonable conversion could be achieved under 50 bar of hydrogen. The conversion strongly depended on the nature of the solvent: no reaction occurred in ethyl acetate and dichloromethane while in an alcoholic solvent reaction was possible. It was also noted that the enantiomeric excess was constant all over the reaction. As expected, a higher temperature gave higher conversion but was detrimental to the ee. The size of the ring influenced dramatically the enantioselectivity of the reaction. While the hydrogenation of the five-members ring **1** yielded the racemic saturated ketone, some enantioselectivity was achieved for the hydrogenation of the six- or seven- members rings **2** and **3** (respectively 14 and 15% in MeOH at room temperature). Another ruthenium complex, DiopRu(Met)$_2$ was tested. Significant conversions were achieved but only racemic products were obtained whatever the substrate.

Due to the lack of enantioselectivity for the hydrogenation of the five-membered ring substrate **1** with ruthenium complexes, we tested some cationic rhodium-based complexes. The influence of the nature of the ligand and the solvent is summarized in Table 2.

Table 2

Hydrogenation of **1** in the presence of different homogeneous rhodium complexes.

Catalyst	P (bar) / t (h)	Conv (%)	ee (%)
BoxRhCOD **8**	1 / 72	62	< 2
DuphosRhCOD **9**	1/ 10	0	-
DuphosRhCOD **9**	10 / 5	95	< 2
DipampRhCOD **10**	5 / 24	100	10 (*S*)

Conditions: 50 mg substrate, 2 mg catalyst, 10 ml MeOH.

The rhodium complexes were more active than the ruthenium complexes and high conversions were observed even at lower pressure. The nitrogen-based complex [BoxRhCOD]BF_4 when tested at atmospheric pressure yielded 62% conversion after 3 days but the hydrogenated product was racemic. Duphos and Dipamp rhodium catalysts are highly efficient for the asymmetric hydrogenation of dehydroamino acid derivatives. In methanol, these two complexes yielded very high conversion under moderate pressure (< 10 bar). The Duphos ligand was non selective and racemic product was obtained. Surprisingly small but significant enantiomeric excess was observed with Dipamp-based complex (*ca*. 10%).

This catalyst was then applied for the hydrogenation of the different substrates (Table 3). As previously observed in the presence of ruthenium catalyst, higher ee's were achieved for the hydrogenation of the six- and seven-membered rings. These rhodium complexes were more active than the ruthenium complexes: under 5 bar of hydrogen the conversion was complete after 6h and the enantiomeric excess reached 20% in MeOH for the six- and the seven-membered ring substrates. In CH_2Cl_2, the hydrogenation rate and the enantioselectivity decreased dramatically.

Table 3

Enantioselective hydrogenation of **1-3** in the presence of catalyst DipampRhCOD **10**

Substrate	Solvent	P (bar) / T (h)	Conv (%)	ee (%) (*S*)
1	MeOH	5 / 24	100	10
2	MeOH	5 / 6	100	20
3	MeOH	5 / 7	100	20
3	MeOH	1 / 24	4	-
3	CH_2Cl_2	5 / 46	100	5

Conditions: 50 mg substrate, 2 mg catalyst, 10 ml solvent

In conclusion, we demonstrated that exocyclic α,β-unsaturated ketones can be reduced to the corresponding saturated ketones with complete chemoselectivity in the presence of ruthenium or rhodium complexes. Mild pressure and temperature conditions are necessary and the best ee's were achieved for the six and the seven-members ring in the presence of $[DipampRhCOD]^+BF_4^-$. Even if the enantioselectivities are moderate, we showed the complementarities between heterogeneous and homogeneous catalysts: over heterogeneous metallic supported catalyst, only the hydrogenation of the seven-membered ring substrate yielded significant enantiomeric excess. As concerns the use of homogeneous catalysts, the six and seven-membered ring substrates yielded similar ee's. In the first case, the enantioselectivity can be correlated to the different adsorption routes of the substrate on the metallic substrate. Molecular modelling calculations showed that the five and the six-members ring substrates are both nearly flat, while the two aromatic rings of the seven-member ring are nearly perpendicular. In the presence of homogeneous catalyst, the ee is connected to the specificity of the chelation of the substrate with the organometallic centre, probably through the carbonyl group. This coordination may be less efficient in the case of the five–membered ring due to steric constraint in the ring.

EXPERIMENTAL

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

2,2'-methylenebis[(4*S*)-4-phenyl-2-oxazoline] (1,5-cyclooctadiene) rhodium (I) tetrafluoroborate **8** was prepared according to ref. 10. Dichloro[(*S*)-(-)-2,2'-bis(diphenyl-phosphino)-1,1'-binaphtyl] ruthenium (II) **7**; (-)(1,2-bis[(2*S*,5*S*)-2,5-dimethyl phospholano]ethane

(1,5-cyclooctadiene) rhodium (I) trifluoromethanesulfonate, **9**; (*R,R*)-(-)-1,2-bis[o-methoxyphenyl)(phenyl)phosphino] ethane (1,5-cyclooctadiene) rhodium (I) tetrafluoroborate **10** complexes were commercial products from Strem Chemicals.

The hydrogenation reactions were carried out in a 30 ml stainless steel autoclave equipped with a magnetic stirrer. Typically, the substrate was dissolved in the solvent. The catalyst was added and the autoclave was purged with nitrogen. Hydrogen was introduced up to the desired pressure and the temperature was increased if necessary. Samples withdrawn from the autoclave were analysed by HPLC (Chiralcel OJ column, heptane/2-propanol 80/20 v/v, flow rate 0.8 ml/min, detection 249 nm).

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