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Asymmetric hydrogenation of prochiral γ-nitroketones by ruthenium complexes

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Abstract

A series of 1-aryl-4-nitro-1-butanones was subjected to asymmetric catalytic hydrogenation in homogeneous phase by using two different ruthenium complexes as chiral catalyst. With (−)-$Ru_4(CO)_8[glu]_2[(+)-DIOP]_3$ the corresponding secondary alcohols **5–7** and **10** were obtained in any case and with ee's ranging from 3 to 40%, whereas with $H_4Ru_4(CO)_8[(+)-DIOP]_2$ the reduction afforded alcohols (12–34% ee) **5–7** or pyrrolidine **9** (3–13% ee) depending on the substitution on the aromatic ring of the nitroketones.

Keywords: Asymmetric hydrogenation; γ-Nitroketones; Ruthenium complexes; Homogeneous catalysis

1. Introduction

The enantioselective reduction of prochiral γ-nitroketones to the corresponding nitroalcohols allows the access to a class of chiral building blocks very useful for the synthesis of a variety of heterocyclic compounds. So far, the reduction of nitroketones mediated by baker's yeast has been the most used way to obtain optically active nitroalcohols [1–6].

Despite the broad applicability and low cost of yeast and of the nutrients of such microbial reductions, some limitations exist when trying to control the stereochemical outcome of the reaction, as well as trying to improve notably the enantiomeric excesses of the desired products by changing the reaction conditions.

Therefore, and because of our ongoing interest in optically active nitroalcohols as precursors for the synthesis of chiral heterocycles such as indolizidines [1], pyrrolidines [2] and spiranes [3], we sought other means of reduction processes, and the homogeneous asymmetric hydrogenation with chiral catalysts, which is novel for the reduction of nitroketones, appeared to be suitable for our purposes.

For the asymmetric hydrogenation of aromatic and aliphatic ketones with ruthenium and rhodium based chiral catalysts it is well established that the best results are achieved when an α or β substituent capable of coordination to the metallic centre is present [7–12].

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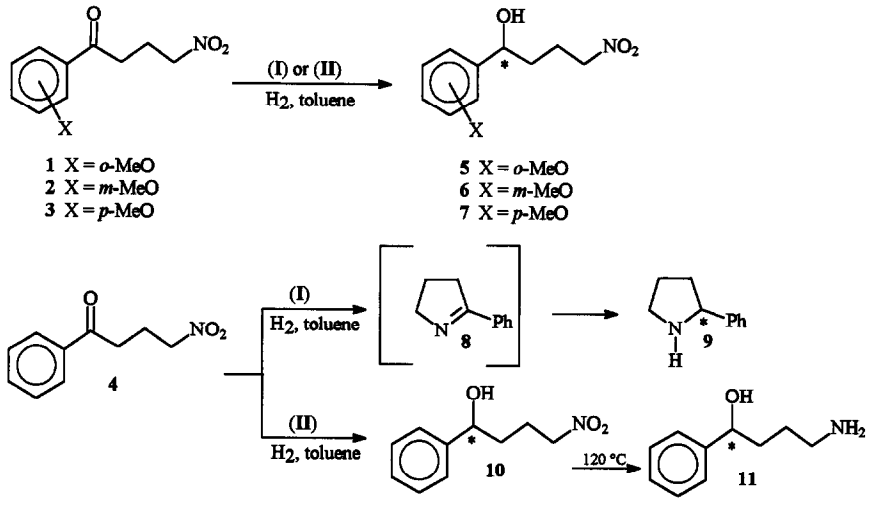

Scheme 1.

Alternatively, the presence in the catalytic medium of tertiary amines could also give rise to secondary alcohols with high ee's [13,14].

In this paper, we report the first application of two ruthenium based chiral complexes as catalyst in the reduction of 1-aryl-4-nitro-1-butanones, for instance $H_4Ru_4(CO)_8[(+)$-DIOP$]_2$ **(I)** and $(-)$-$Ru_4(CO)_8[glu]_2[(+)$-DIOP$]_3$ **(II)** which have already been characterised and used in the homogeneous hydrogenation of aromatic ketones and keto-acids [15–17].

2. Experimental

^{1}H-NMR were recorded in $CDCl_3$ on a Varian Gemini at 200 MHz and on a Bruker DRX 500 MHz. Gas-chromatographic analysis were performed with a Hewlett Packard 5890 A instrument, equipped with a HP1 capillary column (100% methylsilicone, 0.53 mm i.d.). $(-)$-$Ru_4(CO)_8[glu]_2[(+)$-DIOP$]_3$ [17] and $H_4Ru_4(CO)_8[(+)$-DIOP$]_2$ [18] were synthesised as described in the literature. Nitroketones **1–4** were prepared as reported [2]. Compounds

Table 1
Hydrogenation of nitroketones **1–3** to nitroalcohols **5–7** with $H_4Ru_4(CO)_8[(+)$-DIOP$]_2$ [a] **(I)**

Run No.	Substrate	Temp. (°C)	Time (h)	Conversion [b] (%)	Product	Configuration [c]	ee [c]
1	**1**	80	96	30	**5**	*R*	34
2	**1**	120	20	70	**5**	*R*	24
3	**1**	120	48	100	**5**	*R*	22
4	**2**	80	48	43	**6**	*R*	20
5	**2**	120	20	90	**6**	*R*	12
6	**3**	80	48	70	**7**	*R*	28
7	**3**	120	20	100	**7**	*R*	17

[a] Substrate = 2.40 mmol; catalyst precursor = 0.106 mg atoms Ru; toluene as solvent = 25 ml; p_{H_2} = 130 atm at 20°C.
[b] By gas-chromatographic analysis of the crude reaction mixtures.
[c] Determined by ^{1}H-NMR analysis of Mosher ester derivatives.

Table 2
Hydrogenation of nitroketone **4** with $H_4Ru_4(CO)_8[(+)\text{-DIOP}]_2$ [a] (**I**)

Run No.	Temp. (°C)	Time (h)	Conversion [b]	Imine **8** (%)	Pyrrolidine **9** (%)	Configuration [c]	ee [c] (%)
8	40	192	0	–	–		
9	60	48	48	96	4	–	n.d.
10	60	192	100	–	100	*R*	4
11	80	48	75	70	30	–	n.d.
12	80	72	100	50	50	*R*	13
13	100	48	100	38	62	*R*	12
14	120	48	100	–	100	*R*	3

[a] Substrate = 2.40 mmol; catalyst precursor = 0.106 mg atoms Ru; toluene as solvent = 25 ml; p_{H_2} = 130 atm at 20°C.
[b] By gas–chromatographic analysis of the crude reaction mixtures.
[c] Determined by ^{1}H-NMR (500 MHz) analysis of Mosher amide derivatives and comparison of optical rotations: for compound (*R*)-**9** with 76% ee the optical rotation is $[\alpha]_D^{20} = +24.6°$ (*c*, 0.837, MeOH) [2].

5–7, **9–11** [2] and **8** [19] have already been synthesised and their spectroscopic data are identical to those reported in the literature. Mosher ester derivatives of alcohols **5–7** and **10** and amide derivative of pyrrolidine **9** were prepared as reported [20] and analysed by ^{1}H-NMR at 200 and 500 MHz.

The hydrogenation apparatus consists of a magnetically stirred 150 ml stainless steel autoclave equipped with valves and manometer. In a typical experiment, substrate (2.40 mmol) was placed in the autoclave together with the solvent (25 ml) and the ruthenium catalyst (0.106 mg atoms of Ru). The reactor was purged with nitrogen, pressurised with H_2 and heated in a thermostated bath (±0.1°C). After the desired reaction time, the reactor was cooled to room temperature, the residual gas removed and the reaction mixture analysed by GLC and ^{1}H-NMR.

Table 3
Hydrogenation of nitroketones **1–4** with $(-)\text{-}Ru_4(CO)_8[glu]_2[(+)\text{-DIOP}]_3$ [a] (**II**)

Run No.	Substrate	Temp. °C	Time (h)	Conversion [b] (%)	Product	Configuration [c]	ee [c] (%)
15	**1**	40	189	72	**5**	*R*	36
16	**1**	80	12	60	**5**	*R*	34
17	**1**	80	24	90	**5**	*R*	31
18	**1**	80	48	100	**5**	*R*	27
19	**1**	120	20	85	**5**	*R*	30
20	**1**	120	48	100	**5**	*R*	26
21	**1**	120	96	100	**5**	*R*	10
22	**2**	40	112	25	**6**	*R*	10
23	**2**	80	48	76	**6**	*S*	5
24	**2**	120	20	82	**6**	–	0
25	**3**	40	192	20	**7**	*R*	40
26	**3**	80	48	77	**7**	*S*	6
27	**3**	120	20	95	**7**	*S*	3
28	**4**	40	192	72	**10**	*R*	36
29	**4**	80	48	85	**10**	*R*	34
30	**4**	120	48	100	**11**	*R* [d]	3 [d]

[a] Substrate = 2.40 mmol; catalyst precursor = 0.106 mg atoms Ru; toluene as solvent = 25 ml; p_{H_2} = 130 atm at 20°C.
[b] By gas–chromatographic analysis of the crude reaction mixtures.
[c] Determined by ^{1}H-NMR analysis of Mosher ester derivatives.
[d] Determined by comparison of optical rotations: for compound **11** with 78% ee the optical rotation is $[\alpha]_D^{20} = 43.5°$ (*c* 0.53, $CHCl_3$) [2].

3. Results and discussion

The results of our investigations on the regio- and enantioselectivity in the reduction of prochiral γ-nitroketones **1–4** (Scheme 1) are summarised in Tables 1–3.

In Tables 1 and 2 we report the results obtained for the hydrogenation using (**I**) as a catalyst. At 80 and 120°C, nitroketones **1–3** with a methoxy group on the phenyl ring led to the corresponding alcohols with ee's ranging from 12% to 34% and an *R* absolute configuration (runs 1–7). Surprisingly, the hydrogenation of the unsubstituted nitroketone **4** conducted to the imine **8** (runs 9, 11–13) and pyrrolidine **9** (runs 9–14) and not to nitroalcohol **10**. This could be attributed to the initial coordination of the nitro group to the metal and its subsequent reduction to primary amine, followed by a cyclization yielding the imine **8** (Scheme 1). Compound **8** is then reduced to pyrrolidine **9** with an enantioselectivity ranging from 3% to 13% ee and having an *R* absolute configuration. The low values of optical purity of **9** are likely due to the weak binding of the imine intermediate to the catalyst and/or to a possible isomerisation of double bond before reduction [21–23].

In order to appreciate the relative percentage of conversion as well as the relative amounts of imine and pyrrolidine present at the same time and different temperatures, we carried out four experiments (runs 9, 11, 13 and 14), stopping the reactions at 48 h. As expected the conversion increased with the temperature, as well as the relative amount of pyrrolidine, considering that the formation of **9** follows that of imine **8** as depicted in Scheme 1.

When simple aromatic ketones such as acetophenone, ethylphenylketone, propylphenylketone and butylphenylketone underwent catalytic hydrogenation at 120°C in presence of **I**, general low reactivities were observed, as well as very low optical purities of the products ($<$ 1.3%) [15]. Comparing these data to those obtained in the present work, it is possible to suggest that the nitro group of the substrate coordinates to the catalyst leading thus to an enhancement of enantioselectivity. In addition, in absence of a methoxy group on the aromatic ring only the reduction of the nitro group to $-NH_2$ occurred (runs 9–14). This type of reaction has already been observed for unfunctionalised aliphatic nitrocompounds with Rh and Pd based catalysts in homogeneous phase [24–26]. When a substituent such as methoxy group is present on the aromatic ring, the reduction of the carbonyl group is favoured (runs 1–7); even at 120°C for 48 h only (*R*)-**5** is obtained from **1** (run 3). Moreover, when this substituent is at the *ortho* position the highest ee (34%) of the alcohol is obtained (run 1), presumably due to its simultaneous coordination to the metal [8].

In Table 3 (runs 15–30), we report the results of hydrogenation of nitroketones **1–4** in the presence of catalyst **II**. Due to the greater activity of this catalyst [15–17] it was possible now to operate at lower temperatures, and at 40°C ee's up to 40% were observed for the nitroalcohols **5–7** (runs 15, 22, 25) and **10** (run 28), which are the only products recovered in the final reaction mixture.

With catalyst **I**, the same nitroketones **1–4** did not react at all at 40°C. The change of chemoselectivity obtained in the case of **4** when using catalysts **I** and **II** could be related to the different structures of the two catalyst precursors leading to different active species [17]. With catalyst **II**, one of the carboxylate groups of the two bidentate glutarate ligands could be easily replaced by the carbonyl group of the substrate, and reduction to alcohols occurs in any case. With complex **I**, where no glutarate ligand is present, the coordination of the carbonyl group could become more difficult and should be favoured only when the aromatic ring bears a methoxy group.

In compound **4**, the reduction of the nitro group did not occur even at 80°C for 48 h (run 29), but increasing the temperature to 120°C the aminoalcohol **11** was obtained (scheme 1) with an *R* configuration at the carbinolic centre and 3% ee (run 30). The absence in the crude

reaction mixture of imine **8** or pyrrolidine **9** indicated that the carbonyl group is still reduced faster than the nitro group. In nitroketones **1–3** the reduction of the nitro group did never occur at 120°C for 20 h (runs 19, 24, 27). In particular, for nitroketone **1** we forced the hydrogenation conditions with both catalysts **I** and **II**, prolonging the reaction time at the reaction temperature of 120°C, but still only the formation of the corresponding (*R*)-**5** was observed (runs 3, 20 and 21).

Comparing now the results of the hydrogenation of **1**, **2** and **3** at 40, 80 and 120°C with catalyst **II**, it appeared that for **1** the absolute configuration of the hydrogenated product did not change significantly when increasing the temperature and only small changes in the ee of **5** were measured (runs 15, 17 and 19). In contrast, in the reduction of compounds **2** and **3** a strong decrease of ee was observed when increasing the temperature, as well as a change in the enantiofacial discrimination (runs 22–24 and 25–27). These results seem consistent with a higher chelating capability of the *ortho* methoxy group when it is proximal to the carbonyl group. Furthermore, considering both the reversed enantioselectivity at 40 and 80°C in yielding nitroalcohols **6** and **7**, and the identical values of ee obtained for nitroalcohol **10** at 40 and 80°C, different structures of the catalytic active species at the two experimental temperatures must be taken in account.

We observed that the optical purity of nitroalcohol **5** does not depend markedly on the conversion. In fact, with catalyst **II**, nitroketone **1** at 80°C in only 12 h (run 16) gave (*R*)-**5** with 60% conversion and 34% ee After 24 h (run 17), the ee of **5** was not very different (31% ee and 90% conversion) as well as after 48 h (27% ee at 100% conversion) (run 18). The same behaviour was observed operating at 120°C: after 20 h (85% conversion) the ee of (*R*)-**5** was 30%; after 48 h when conversion was complete, ee decreased to 26%, but after very long reaction time (96 h) it dropped to 10% (run 21). These results are consistent with a possible racemization of the nitroalcohol due to the high temperature and to the prolonged reaction time.

4. Conclusions

Keeping in mind our initial purpose, that was to find an alternative route to optically pure nitroalcohols, we can conclude that the homogeneous hydrogenation of nitroketones with the two catalyst precursors **I** and **II** did not give very satisfactory results in terms of optical purities of the produced nitroalcohols. Nevertheless, a surprising increase of enantioselectivity related to the presence of the nitro group was observed if we compare the ee's obtained with the γ-nitroketones tested in this work with those reported for simple arylketones.

Moreover, this work showed an interesting case of hydrogenation chemoselectivity between a carbonyl and a nitro group both present in the substrate, depending on the presence of the methoxy substituent on the phenyl ring.

At the present, experiments using other chiral ligands and/or different mono nuclear metal complexes are in progress in order to improve the enantioselectivity in the homogeneous hydrogenation of γ-nitroketones.

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