Tetrahedron Vol. 44, No. 5, pp. 1409 to 1412, 1988
Printed in Great Britain.

0040-4020/88 $3.00+.00

CATALYTIC ASYMMETRIC SYNTHESES.
Part III. Asymmetric Hydrogenation of Piperitenone Catalysed by Chiral Ruthenium Hydrides : An Example of a Catalytic Kinetic Resolution[1].

Paul LE MAUX, Viviane MASSONNEAU and Gérard SIMONNEAUX*

Laboratoire de Chimie des Organométalliques, UA CNRS 415,
Université de Rennes I, 35042 Rennes Cedex, France

(*Received in Belgium* 14 *December* 1987)

Abstract - Piperitenone has been hydrogenated in the presence of chiral ruthenium catalysts to give piperitone, menthone and isomenthone. Starting from piperitone (42 % e.e.) excellent selectivity (≃ 80 % e.e.) was obtained with menthone. The mechanism of the reaction, a double asymmetric synthesis, is discussed with respect to kinetic resolution of piperitone as well as the effect of the chiral center in the substrate on the catalytic asymmetric induction.

Monoterpenes of known absolute configuration are particularly attractive chiral starting materials for the synthesis of more complex natural products[2]. Examples include pulegone and piperitenone which are useful compounds in this respect[3]. However, few examples are known of asymmetric catalytic process in which such optically active ketones have been prepared since most of the catalytic hydrogenation routes have been focused to the synthesis of aminoacids[4]. In a previous paper, we reported that $HRuCl(TBPC)_2$|(-),RR,trans-1,2-bis((diphenylphosphino)methyl)cyclobutane|[5] is an effective catalyst for the asymmetric hydrogenation of carbon-carbon double bonds present in α,β-unsaturated ketones[1]. Saturated, optically active ketones were obtained by this procedure from prochiral substrates. We have now extended our investigation on the catalytic activity of $HRuCl(TBPC)_2$ to the reduction of piperitenone, in order to examine the possibilitiy of a double asymmetric hydrogenation of a substrate containing two prochiral carbon-carbon double bonds[6].

RESULTS AND DISCUSSION

Piperitenone 1 has been previously hydrogenated with chiral rhodium catalysts giving predominantly pulegone 3 with 38 % enantiomeric excess (e.e.)[7]. Surprisingly, using ruthenium catalysts we found that the more substituted double bond of 1 was first hydrogenated leading to formation of (S)-piperitone 2. The results are summarized in table 1.

High selectivity to piperitone 2 during the first step could be obtained easily when the reaction was performed at various advancements. However, the amount of menthone-isomenthone increased with time to a large extent. Moreover the e.e. of 2 diminished with conversion whereas that of menthone and isomenthone became enhanced. The used of $Ru_2Cl_4((Diop)_3$|(-)RR,2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane| as catalyst[8] was also explored but the e.e. of 2 was slightly decreased (entry 4). For purpose of comparison, results with a chiral cobalt complex[9] have been also included (entry 5). In this case (-) pulegone 3 was formed with low e.e. (15 %).

Table 1. Asymmetric hydrogenation of piperitenone[a] (Scheme 1)

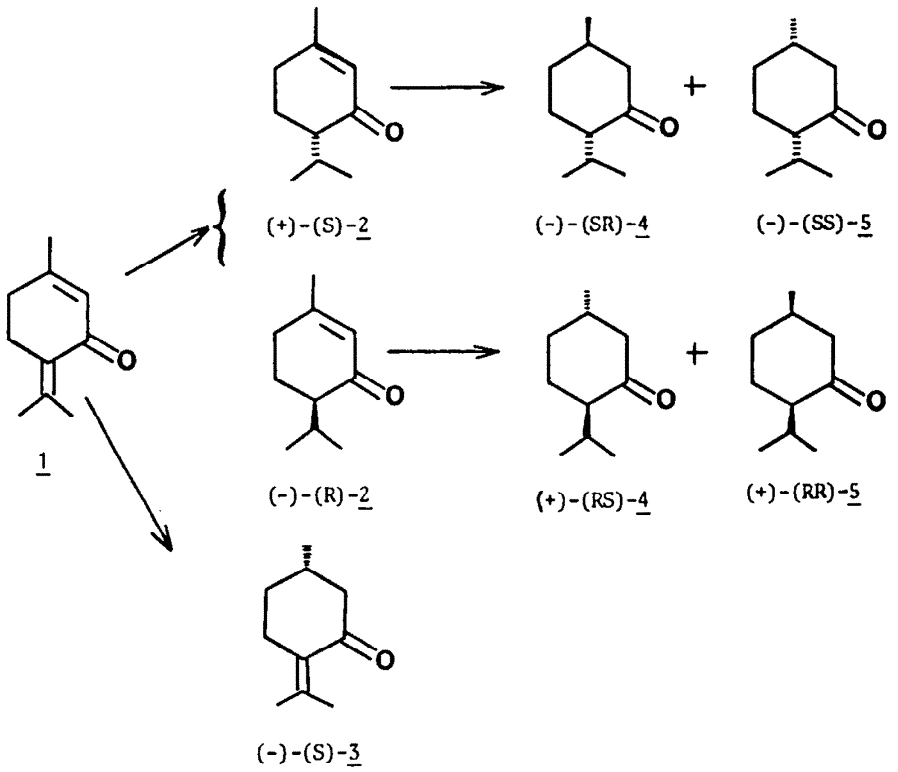
Entry	Catalyst[b]	Conversion % (time, h)	Pulegone 3 %	Piperitone 2 %	% ee(S)	Menthone 4 %	% ee(SR)	Isomenthone 5 %	% ee(RR)
1	A	20 (12)	2	16	42	1.5	-	0.5	-
2	A	69 (30)	2.5	46	39	13.5	55	7	31
3	A	82 (48)	3.5	48.5	26	21	62	9	37
4	B	52 (30)	2	40	35	7	-	3	-
5	C	64 (26)	55[c]	6	-	2	-	1	-

[a] 50/1 substrate/catalyst, solvent : toluene, 10 atm H_2 and 60° (entry : 1, 2, 3), 65° (entry 4, 5)

[b] A : $HRuCl(TBPC)_2$[5] ; B : $Ru_2Cl_4(Diop)_3$[8] ; C : $Co_2(CO)_6|P(Ph)_2Neomenthyl|_2$[9]

[c] 3 (S)ee : 15 %

Scheme 1



The former results could be interpreted by assuming a kinetic resolution in the second step of the reaction[10] in which the major S isomer of piperitone 2 (+) is rapidly hydrogenated to a mixture of menthone and isomenthone. This may be the reason why the decrease of the enantiomeric excess of (+) 2 was observed with time. However a simple racemization of the substrate may also explained the result : owing to the fact that optically active piperitone undergoes very easily partial or complete racemization during isolation[11].

In this context, we further looked at the effect of the new formed substrate chiral center on the catalytic asymmetric reaction by using racemic 2 as substrate and $HRuCl(TBPC)_2$ as chiral catalyst. Results are listed in table 2.

Table 2. Asymmetric hydrogenation of racemic piperitone in presence of $HRuCl(TBPC)_2$[a] (Scheme 1)

Entry	Conversion % (time, h)	Stereoisomers %			Enantiomeric excess %			a	b
		2[b]	4	5	2-(R)	4-(SR)	5-(RR)		
1	26 (20)	74	17.5	8.5	3 (-)	28.5(-)	37.5(+)	0.93	0.24
2	56 (48)	44	39	17	13.5(-)	35 (-)	51 (+)	1.03	0.16
3	75 (78)	25	50	25	20 (-)	43.5(-)	66.5(+)	1.43	0.11

[a] 50/1 substrate/catalyst, solvent : toluene, 10 atm H_2 and 60°
[b] recovered starting piperitone

As table 2 shows, the catalyst is sensitive to the preexisting chirality in the substrate : the hydrogenation of racemic 2 proceeds more rapidly with one of the enantiomers ((+)-S-2). Accordingly, the e.e. of the recovered starting material, predominantly the R enantiomer, is enhanced with time. The most obvious explanation for the decrease of the e.e. with conversion (table 1, entries 1,2,3) during the first step of hydrogenation (1 → 2) is the kinetic resolution occuring during the second step (2 → 4 + 5). It should be also noted that the e.e. of 4 and 5 increases with time.

In order to understand more deeply the origin of the e.e. of each diastereoisomer (4 and 5), we applied a relationship between the relative amounts and the e.e. of reaction products and recovered starting material, recently proposed by Kagan and Coll.[12]. There are no major discrepancies between experimental data and calculated values from equation $Y_0 = X_1Y_1 + X_2Y_2 + X_3Y_3$ (Y_0 : e.e. of starting 2 (=0) ; Y_1 e.e. of 2 after kinetic resolution ; Y_2 and Y_3 e.e. of respectively isomenthone 5 and menthone 4 ; X_1, X_2, X_3 represent the fraction amount after partial conversion of one mole). For example, with 56 % conversion, the equation leads to Y_1 calc. : 11 % and Y_1 meas. : 13.5 %. These results suggest the absence of racemization of 2 during the reaction.

To realize the extent of enantioface differentiation more quantitatively, we must look at the ratio of diastereoisomers (+)5/(+)4 = a and (-)5/(-)4 = b. As pointed out by Kagan[12], these ratio are independant of time if the structure of the chiral catalyst remains constant throughout the reaction. Values are summarized in table 2. It clearly appears that the stereoselectivities are slightly conversion-dependent. This phenomenon which has been previously detected for the first time during hydrogenation of dehydropeptides[12] may be quite general. It can be interpreted as the indication that several catalytic species are involved in the reaction.

Finally, we carried out the reduction of 2 with (+)2 form predominating (e.e. : 42 %). As expected, the e.e. of (-)4 is high (80 %) and the e.e. of the recovered 2 is lower than that of the starting material (table 3, entry 1). We checked also the influence of the chiral center in the substrate on asymmetric induction. The experiment using an achiral phosphine ligand PPh_3 $|RuCl_2(PPh_3)_3|$[13] gave the consistent result (table 2, entry 2) : the e.e. of the reduced products was identical to that observed for piperitone 2. In this case, no asymmetric induction which favored the formation of one of the diastereoisomers was observed.

CONCLUSION

The high values of the e.e. (55-80 %) obtained with 4 from the reduction of piperitenone or piperitone have been attributed in large part to the kinetic resolution. The modest results usually obtained in asymmetric hydrogenation of α-β unsaturated ketones, due to the low rigidity of the catalytic intermediate can be increased by double asymmetric synthesis.

Table 3. Asymmetric hydrogenation of optically active piperitone[a]

Entry	Catalyst	Enantiomeric excess % 2[b]	4	5
1	$HRuCl(TBPC)_2$	34(+)-(S)	80(-)-(SR)	25(+)-(RR)
2	$RuCl_2(PPh_3)_3$[c]	29(+)-(S)	30(-)-(SR)	31.5(-)-(SS)

[a]Values of enantiomeric excess of starting piperitone are 42 % and 29.5 % of entries 1 and 2 respectively.
Conditions are the same as indicated in table 1 and 2 (time : 24 h).

[b]Recovered starting piperitone.

[c]See reference 13.

EXPERIMENTAL SECTION

The following instruments were used : Bruker AW 80 NMR spectrometer ; Unicam SP 1100 spectrophotometer ; Perkin-Elmer 241 polarimeter. An Intersmat system (column : carbowax 1540, l=18 m, Ø=0.5 mm) was used for GC analysis. Piperitone was prepared by catalytic hydrogenation of piperitenone using $RuCl_2(PPh_3)$[13]. Piperitone, menthone and isomenthone for determination of optical purity were obtained by preparative column chromatography on silica gel eluted with a mixture of ether/hexane (1:10). (In practice, pure menthone and isomenthone are very difficult to obtain. A second chromatography gives a good separation of the menthone-isomenthone mixture). Enantiomeric excesses are calculated relative to the published values for the optically pure compounds 2 : reference 11 ; 4 and 5 : reference 14.

The reactions were carried out in a 300 mL Engineer autoclave with a magnetic stirrer[1].

REFERENCES

1. For Part II, see : V. Massonneau, P. Le Maux and G. Simonneaux, J. Organometal. Chem., 1987, 327, 269.
2. W.A. Szabo and H.T. Lee, Aldrichimica Acta, 1980, 13, 13.
3. A.F. Thomas, The Total Synthesis of Natural Products, edited by Apsimon, 1973, vol. 2, pp 118-123.
4. H.B. Kagan, in G. Wilkinson (Ed.), Comprehensive Organometallic Chemistry, Pergamon Press, Oxford, 1982, vol. 8, p 463.
5. V. Massonneau, P. Le Maux, R. Dabard, G. Simonneaux, P. Aviron-Violet and T.P. Dang, Inorg. Chem., 1987, 26, 773.
6. J.J. Beereboom, J. Org. Chem., 1966, 31, 2026.
7. J. Solodar, J. Org. Chem., 1978, 43, 1787.
8. B.R. James, R.S. McMillan, R.H. Morris and D.K. Wang, Adv. Chem. Ser., 1978, 167, 122.
9. P. Le Maux, V. Massonneau and G. Simonneaux, J. Organometal. Chem., 1985, 84, 101.
10. J.M. Brown and I. Cutting, J. Chem. Soc. Chem. Commun., 1985, 578.
11. A.J. Burbott, J.P. Hennessey, Jr., W. Curtis Johnson and Jr., W.D. Loomis, Phytochem., 1983, 22, 2227.
12. S. El-Baba, J.C. Poulin and H.B. Kagan, Tetrahedron, 1984, 40, 4275.
13. T.A. Stephenson and G. Wilkinson, J. Inorg. Nucl., 1966, 28, 945.
14. J. Read and R.G. Johnston, J. Chem. Soc., 1934, 226.