ENANTIOSELECTIVE SYNTHESIS OF β-HYDROXYAMIDES *VIA* ASYMMETRIC HYDROGENATION OF β-KETOAMIDES USING CHIRAL Ru(II)-CATALYSTS

T. Gmiza [a], R. Touati [a], C. Deport [b], V. Ratovelomanana-Vidal [b], J.-P. Genet [b], B. Ben Hassine [a] *

[a] *Laboratoire de Synthèse Organique Asymétrique et Catalyse Homogène, Faculté des Sciences de Monastir, Avenue de l'Environnement, 5019 Monastir, Tunisie*
[b] *Laboratoire de Synthèse Sélective Organique et Produits Naturels, UMR 7573 CNRS, Ecole Nationale Supérieure de Chimie de Paris, 11 Rue P. et M. Curie, 75231 Paris Cedex 05, France*

(Reçu le 20 Janvier 2006, accepté le 27 Avril 2006)

ABSTRACT: Asymmetric hydrogenation of β-ketoamides **1a-i** using chiral Ru(II)-catalysts with BINAP, MeO-BIPHEP, SYNPHOS and DIFLUORPHOS as atropisomeric ligands leads to the corresponding β-hydroxyamides **2a-i** with good chemical yields (75% to 95%) and high enantioselectivities (73% to 99%) under 5 to 10 bar of hydrogen pressure.

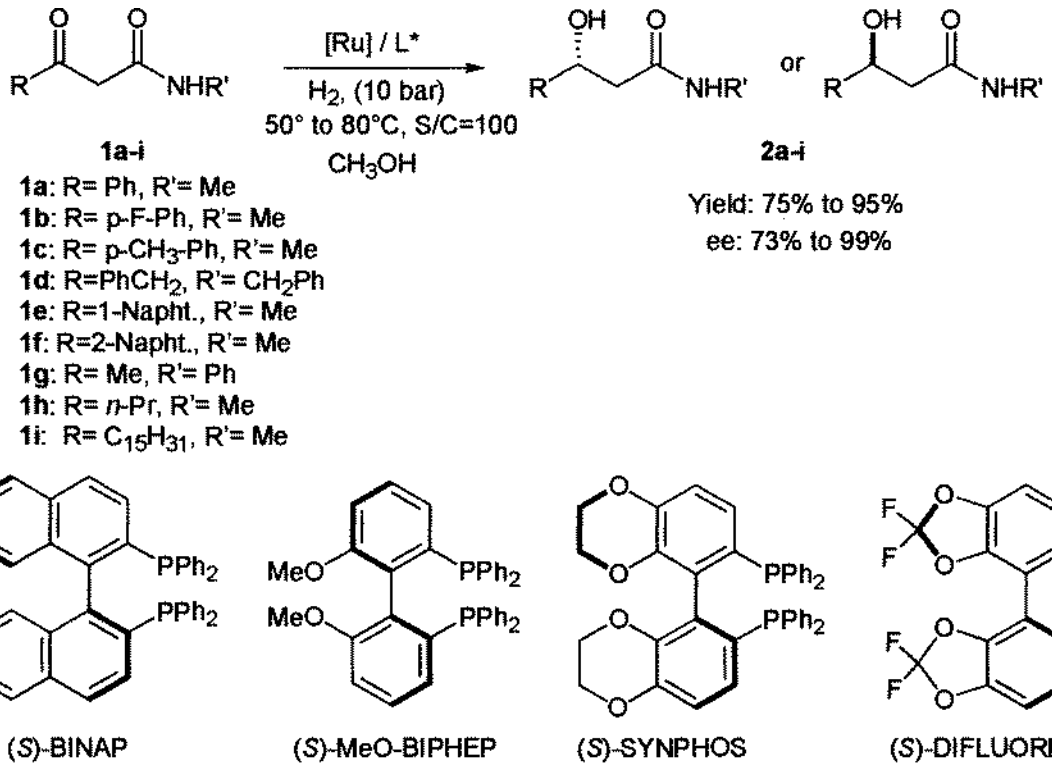
Keywords : catalysts, ruthenium, hydrogenation, enantioselectivity

RESUME: L'hydrogénation asymétrique d'une série de β-cétoamides **1a-i** en présence des catalyseurs chiraux de Ru(II) associés aux ligands BINAP, MeO-BIPHEP SYNPHOS et DIFLUORPHOS conduit aux β-hydroxyamides correspondants **2a-i** avec de bons rendements chimiques (75% à 95%) et des excès enantiomériques élevés (73% à 99%) sous une pression de 5 à 10 bar.

INTRODUCTION

Catalytic asymmetric synthesis is a valuable method to prepare biologically active substances[1-5] in enantiomerically pure form. Enantioselective catalysis using chiral transition metal complexes appears as one of the most efficient method since a small amount of material can, in principle, produce a large amount of optically actives products. Although the β-hydroxyamides are useful synthetic intermediates, there are only few efficient methods for the enantioselective synthesis of such intermediates.[6-8] Chiral β-hydroxyamides are essential as starting materials for the preparation of chiral 1,3-aminoalcohols and β-lactams used on a large scale in organic chemistry as chiral units of synthetic utility.[9,10] Moreover, they have many applications in the synthesis of both pharmaceutical intermediates and biologically active compounds.[11,12]
We recently reported that (*R*)-SYNPHOS[13] and (*R*)-DIFLUORPHOS[14] are efficient ligands for the asymmetric hydrogenation of β-ketoamides by chiral ruthenium complexes.[15] In this paper, we report further results from an ongoing systematic examination of different chiral ligands used in the ruthenium catalysed asymmetric hydrogenation (scheme 1). In all cases, complete conversions have been achieved (Table I).

* corresponding author, fax: + 216 73 500 278, e-mail: bechirbenhassine@yahoo.fr



Scheme 1

RESULTS AND DISCUSSION

β-ketoamides **1a-c** and **1e-i** have been prepared according to the literature[16,17] by condensation of methylamine with various β-ketoesters in refluxing THF. The (*N*-benzyl-3-oxo-3-(benzyl)propanamide **1d** has been prepared by condensation of phenylacyl Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione)derivative with benzylamine in refluxing benzene. Asymmetric hydrogenation of β-ketoamides **1a-i** has been performed in methanol at a temperature varying from 50°C to 80°C and under a 5 to 10 bar hydrogen pressure using different chiral Ru(II) catalysts (Table I). The Ru-catalysts have been prepared in *situ* from a mixture of (Cod)Ru(2-methylallyl)$_2$ and a chiral diphosphine ligand by addition of HBr according to our convenient and versatile procedure[18a] or by mixing the chiral ligand and the precursor complex [RuCl$_2$(*p*-cymene)]$_2$[18b-d]

As a preliminary attempt to determine the best experimental reaction conditions, we have examined the ruthenium-promoted hydrogenation of *N*-methyl-3-oxo-3-phenylpropanamide **1a** (entries 1-8). All the hydrogenation reactions have been carried out on a mmol scale. The reaction was first conducted by using [RuBr$_2$((*S*)-SYNPHOS)] catalyst at low pressure (5 bar) and 50°C for 10 hours (entry 1), the β-hydroxyamide **2a** has been obtained in 76% yield and 96% ee. By increasing the hydrogen pressure to 10 bar at 50°C, **2a** has been synthesized with both excellent yield and enantioselectivity after only 3 hours (entry 2, 93% yield, 95% ee). Comparable results were obtained for the hydrogenation reaction of **1a** promoted by ruthenium-BINAP complexes. (entry 3, 90% yield, 94% ee). We found that the use of (*S*)-DIFLUORPHOS or (*R*)-MEO-BIPHEP gave good yields and ee of **2a** after 8 hours of reaction time (entries 5 and 6, respectively 90% and 94% yield, 96% and 93% ee). On the contrary, when [Ru(*p*-cymene)((*S*)- SYNPHOS)Cl]Cl was used as a catalyst, lower enantioselectivity and yield were obtained after 10 hours (entry 7, 75% yield, 87% ee). When [(RuCl((*R*)-SYNPHOS))$_2$(μCl)$_3$][NH$_2$Me$_2$] was used as chiral Ru-catalyst, very high level of yields and selectivities were achieved both on 1 to 7 mmol scale (respectively entries 4 and 8, 95 and 92% yields, 99 and 98 ee). Hydrogenation of 3-(*p*-fluorophenyl)-*N*-methyl-3-oxopropanamide **1b** under 5 bar of hydrogen pressure after 10h catalysed by the [RuBr$_2$((*S*)-SYNPHOS)] (entry 9) has given the corresponding β-hydroxyamide **2b** with 76% yield and 96%

ee. By increasing the pressure to 10 bar, the reaction proceeded smoothly with both excellent 91% yield and 96% ee (entry 10). But when we have used ruthenium-BINAP complex a moderate yield and enantioselectivity have been obtained (entry 11, 87% yield, 83% ee). In order to assess the nature of the best catalyst, we have carried out the reactions by using [(RuCl((*S*)-MeO-BIPHEP))$_2$(μCl)$_3$][NH_2Me_2], [(RuCl((*S*)-SYNPHOS))$_2$(μCl)$_3$][NH_2Me_2], [$RuBr_2$((*S*)-DIFLUORPHOS)] and [$RuBr_2$((*R*)-MeO-BIPHEP)] as a catalyst (entries 12-15, respectively 88%, 92%, 92% and 93% yield, 92%, >99%, >99% and 94% ee). High enantioselectivities and good yields have also been observed when the phenyl ring was substituted with a methyl group in the *para*- position (entries 16-20). The corresponding β-hydroxyamide **2c** was synthesized with high selectivities both with [$RuBr_2$((*S*)-SYNPHOS)], [(RuCl((*R*)-SYNPHOS))$_2$(μCl)$_3$][NH_2Me_2], [$RuBr_2$((*S*)-DIFLUORPHOS)] and [$RuBr_2$((*S*)-MeO-BIPHEP)] (entries 16-19), compared with [$RuBr_2$((*S*)-BINAP)], (entry 20, 87% and 73% ee). Tbe hydrogenation reaction of 3-benzyl-*N*-benzyl-3-oxopropanamide **1d**, was also influenced by the nature of the ligand. This compound was reduced to the corresponding β-hydroxyamide **2d** with a better enantioselectivity using (*R*) or (*S*)-SYNPHOS (entries 21 and 22, respectively 89% and 90% yield, 97% and 98% ee) and (*R*)-DIFLUORPHOS (entry 24, 91% yield, 97% ee) compared with the use of (*S*)-MeO-BIPHEP and (*R*)-BINAP (entry 25, 87% yield, 95% ee). Once again, quantitative conversions to enantiomerically-enriched β-hydroxyamides by hydrogenation of 3-hydroxy-3-*N*-methyl-(1-naphthyl)-propanamide **1e** and 3-hydroxy-3-*N*-methyl-(2-naphtyl)-propanamide **1f** (entries 26-33) have been observed under the same catalytic conditions.

This study has been extended to a series of alkyl β-ketoamides (**1g**, **1h**, **1i**) by using Ru-SYNPHOS or Ru-DIFLUORPHOS as chiral catalysts (entries 34-42). In all cases, complete conversions bave been achieved. All hydrogenations have exhibited both an excellent level of enantioselectivities (up to 99%) and yields (90-94%) and can be applied to a high range of substrates. The absolute configuration of the chiral 3-hydroxy-*N*-methyl-3-phenyl propanamide **2a** was assigned from $[\alpha]_D$ values by comparison with known compounds.[8] As far as the other substrates are concerned, we assumed that their hydrogenation followed the same stereochemical course as mentioned above according to the stereochemical model proposed for tbe hydrogenation reaction of carbonyl derivatives with ruthenium-arylphosphine catalysts.[19] This was confirmed by the X-Ray structure of 3-hydroxy-*N*-metbyl-3-(*p*-methylphenyl)propanamide **2c** (fig. 1) which was synthesized from the corresponding β-ketoamide **1c** using the [(RuCl((*R*)-SYNPHOS))$_2$(μCl)$_3$][NH_2Me_2] as a chiral catalyst (entry 17). For details of the X-ray studies see experimental section (12°/), table II and table III.

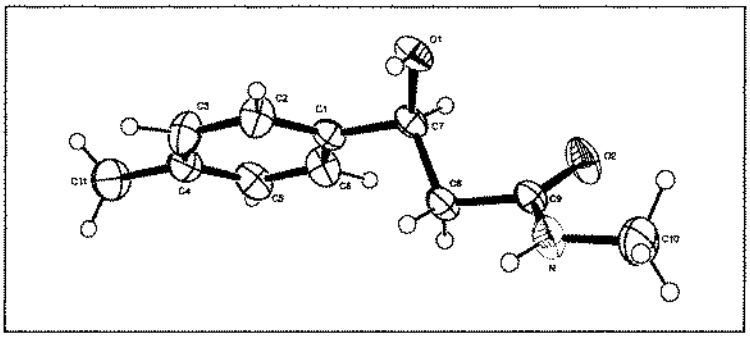
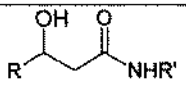


Figure 1: ORTEP[20] drawing of (*S*)-3-Hydroxy-3-(4-methylphenyl)-*N*-methylpropanamide **2c**. Thermal ellipsoids are scaled to enclose 50% probability (see experimental section).

Table I: Asymmetric hydrogenation of β-ketoamides with chiral Ru (II) catalyst[a]

Entry	[Ru]-catalyst	[S][b]	T (°C)	Time (h)	Yield[c] (%)	Products	ee [d](%) (conf.)
							
1	$[RuBr_2((S)\text{-SYNPHOS})]$	**1a**[b]	50	10	76	R= Ph, R'= Me	96 (*R*)
2	$[RuBr_2((S)\text{-SYNPHOS})]$	**1a**	50	3	91	**2a**	96 (*R*)
3	$[RuBr_2((S)\text{-BINAP})]$	**1a**	50	15	90	"	94 (*R*)
4	$[(RuCl((R)\text{-SYNPHOS}))_2(\mu Cl)_3][NH_2Me_2]$	**1a**	50	2	95	"	99 (*S*)
5	$[RuBr_2((S)\text{-MeO-BIPHEP})]$	**1a**	50	8	90	"	96 (*R*)
6	$[RuBr_2((S)\text{-DIFLUORPHOS})]$	**1a**	50	8	94	"	93 (*R*)
7	[Ru(pCy)(*S*)SynphosClCl	**1a**	50	10	75	"	87 (*R*)
8	$[(RuCl((S)\text{-SYNPHOS}))_2(\mu Cl)_3][NH_2Me_2]$	**1a**	50	2	92[e]	"	98 (*R*)
9	$[RuBr_2((S)\text{-SYNPHOS})]$	**1b**[b]	50	19[e]	78	R= *p*-F-Ph, R'= Me	82 (*R*)
10	$[RuBr_2((S)\text{-SYNPHOS})]$	**1b**	50	1	91	**2b**	>99 (*R*)
11	$[RuBr_2((S)\text{-BINAP})]$	**1b**	80	1	87	"	73 (*R*)
12	$[(RuCl((S)\text{-MeO-BIPHEP}))_2(\mu Cl)_3][NH_2Me_2]$	**1b**	50	5	88	"	92 (*R*)
13	$[(RuCl((R)\text{-SYNPHOS}))_2(\mu Cl)_3][NH_2Me_2]$	**1b**	50	1	92	"	>99 (*S*)
14	$[RuBr_2((R)\text{-DIFLUORPHOS})]$	**1b**	50	5	92	"	>99 (*S*)
15	$[RuBr_2((R)\text{-MeO-BIPHEP})]$	**1b**	80	1	90	"	94 (*S*)
16	$[RuBr_2((S)\text{-SYNPHOS})]$	**1b**	50	5	92	R=*p*-CH_3-Ph, R'=Me	99 (*R*)
17	$[(RuCl((R)\text{-SYNPHOS}))_2(\mu Cl)_3][NH_2Me_2]$	**1c**	50	5	93	**2c**	>99 (*S*)
18	$[RuBr_2((S)\text{-DIFLUORPHOS})]$	**1c**	50	19[e]	91	"	94 (*R*)
19	$[RuBr_2((S)\text{-MeO-BIPHEP})]$	**1c**	50	19[e]	93	"	98 (*R*)
20	$[RuBr_2((S)\text{-BINAP})]$	**1c**	50	19[e]	87	"	73 (*R*)
21	$[RuBr_2((R)\text{-SYNPHOS})]$	**1d**	80	5	89	R=$PhCH_2$,R'=CH_2Ph	97 (*R*)
22	$[RuBr_2((S)\text{-SYNPHOS})]$	**1d**	80	5	90	**2d**	98 (*S*)
23	$[RuBr_2((S)\text{-MeO-BIPHEP})]$	**1d**	50	18[e]	89	"	90 (*S*)
24	$[RuBr_2((R)\text{-DIFLUORPHOS})]$	**1d**	80	5	91	"	97 (*R*)
25	$[RuBr_2((R)\text{-BINAP})]$	**1d**	80	18[e]	87	"	95 (*R*)
26	$[RuBr_2((S)\text{-SYNPHOS})]$	**1e**	80	1	93	R=1-NaPht,R'= Me	94 (*R*)
27	$[RuBr_2((S)\text{-SYNPHOS})]$	**1e**	50	1	91	**2e**	>99 (*R*)
28	$[RuBr_2((S)\text{-BINAP})]$	**1e**	50	5	94	"	99 (*R*)
29	$[RuBr_2((S)\text{-DIFLUORPHOS})]$	**1e**	50	5	89	"	>99 (*R*)
30	$[(RuCl((S)\text{-MeO-BIPHEP}))_2(\mu Cl)_3][NH_2Me_2]$	**1e**	50	5	88	"	92 (*R*)
31	$[(RuCl((R)\text{-SYNPHOS}))_2(\mu Cl)_3][NH_2Me_2]$	**1e**	50	2	93	"	>99 (*S*)
32	$[(RuCl((R)\text{-SYNPHOS}))_2(\mu Cl)_3][NH_2Me_2]$	**1f**	50	2	91	R=2-NaPht, R'= Me	93 (*S*)
33	$[RuBr_2((S)\text{-SYNPHOS})]$	**1f**	50	5	92	**2f**	89 (*R*)
34	$[(RuCl((R)\text{-SYNPHOS}))_2(\mu Cl)_3][NH_2Me_2]$	**1g**	50	1	92	R= Me, R'= Ph	99 (*R*)
35	$[(RuCl((S)\text{-SYNPHOS}))_2(\mu Cl)_3][NH_2Me_2]$	**1g**	50	1	94	**2g**	99 (*S*)
36	$[RuBr_2((R)\text{-DIFLUORPHOS})]$	**1g**	50	4	90	"	96 (*R*)
37	$[(RuCl((R)\text{-SYNPHOS}))_2(\mu Cl)_3][NH_2Me_2]$	**1h**	50	0.5	91	R= n-Pr, R'= Me	>99 (*R*)
38	$[(RuCl((S)\text{-SYNPHOS}))_2(\mu Cl)_3][NH_2Me_2]$	**1h**	50	0.5	92	**2h**	>99 (*S*)
39	$[RuBr_2((R)\text{-DIFLUORPHOS})]$	**1h**	50	5	90	"	99 (*R*)
40	$[(RuCl((R)\text{-SYNPHOS}))_2(\mu Cl)_3][NH_2Me_2]$	**1i**	50	1	92	R= n-$C_{15}H_{31}$, R'= Me	>99 (*R*)
41	$[(RuCl((S)\text{-SYNPHOS}))_2(\mu Cl)_3][NH_2Me_2]$	**1i**	50	1	94	**2i**	>99 (*S*)
42	$[RuBr_2((R)\text{-DIFLUORPHOS})]$	**1i**	50	4	93	"	96 (*R*)

(a) 1mmol scale with MeOH as solvent (2 mL). (b) [S] = substrate. (c) Isolated yields by flash chromatography (d) Enantiomeric excesses were determined by HPLC analysis [Chiracel OJ (a cellulose ester) and Chiracel OD-H (a cellulose carbamate) (see experimental section)]. (e) Reaction was conducted on 1.5 g scale.

Experimental Section

General Remarks: Melting points were measured with an Electrothermal-Engineering-LTD-9026 and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker AM 300 spectrometer. Spectra were recorded in deuteriated chloroform and chemical shifts are reported in parts per million (ppm) with TMS as an internal reference. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. Infrared spectra were taken on a Perkin-Elmer 147G spectrometer. All solvents were freshly-distilled, stored under argon and degassed by 3-purge cycles of vacuum/argon at room temperature prior to use. Optical purity (%ee) was determined by HPLC [Chiracel OJ (a cellulose ester) and Chiracel OD-H (a cellulose carbamate)] using an UV detector (λ=215nm et λ=254 nm) at a flow rate of 1.0 mL/mn. The mobile phase and retention times are indicated below for each β–hydroxyamide.

Synthesis of β-ketoamides

Procedure A

A solution of β-ketoester (10 mmol) and methylamine (10 mL, 40% in water) in THF (20 mL) has been heated at 65°C for 3 h. After cooling, the solution has been diluted with ether, washed with saturated aqueous sodium bicarbonate and brine and dried with anhydrous sodium sulfate. The solvent has been evaporated under reduced pressure and the residue obtained has been purified by column chromatography on silica gel [cyclohexane/ ethyl acetate: 80/20]

1°/ *N*-methyl-3-oxo-3-phenylpropanamide 1a

Yield: 91% ; a white solid; mp= 80-81°C ; ^{1}H NMR ($CDCl_3$) δ= 3.96 (s, 2H), 2.86-3.02 (d, 3H, J=4.8Hz), 7.36-7.86 (m, 5H), 8.02 (br, 1H), ; ^{13}C NMR ($CDCl_3$) δ= 26.3, 45.1, 128.3, 128.8, 134.0, 136.1, 166.3, 196.2.

2°/ 3-(*p*-Fluorophenyl)- *N*-methyl-3-oxo-propanamide 1b

Yield: 75% ; a white solid; mp= 116-118°C ; ^{1}H NMR ($CDCl_3$) δ= 2.88-2.94 (d, 3H, J=4.8Hz), 3.96 (s, 2H), 7.07 (br, 1H) , 7.10-7.23 (d, 2H), 8 .04-8.11 (m, 2H) ; ^{13}C NMR ($CDCl_3$) δ= 26.8, 45.8, 116.2, 116.5, 131.7, 131.8, 132.9, 164.9, 166.6, 166.6, 168.3, 194.7 ; MS (70 ev) : m /z= 195 (M^+, 43) ; 165 (12) ; 123 (100) ; 95 (62) .

3°/ *N*-methyl -3-oxo-3-(4-methylphenyl)propanamide 1c

Yield: 88% ; a white solid; mp= 94-95°C ; ^{1}H NMR ($CDCl_3$) δ= 2.28 (s, 3H), 2.80-2.82 (d, 3H, J=4.8Hz), 6.22 (br, 1H) , 7.10-7.13 (d, 2H, J= 8.1Hz) , 7.22-7.25 (d, 2H, J= 8.1Hz) ; ^{13}C NMR ($CDCl_3$) δ= 43.6, 47.9, 50.8, 127.5, 128.6, 129.0, 129.5, 132.8, 137.8, 165.3, 204.4 ; MS (70 ev) : m /z= 191 (M^+, 35) ; 119 (100) ; 91 (90) ; 65 (60)

4°/ *N*-methyl -3-(1-naphtyl) -3-oxopropanamide 1e

Yield: 91% ; a white solid; mp= 102-104°C ; ^{1}H NMR ($CDCl_3$) δ= 2.88-2.89 (d, 3H, J=4.8Hz), 4.04 (s, 3H), 7.09 (br, 1H) , 7.44-7.65 (m, 3H), 7.84-8.36 (m, 3H), 8.66-8.69 (d, 1H, J=9Hz); ^{13}C NMR ($CDCl_3$) δ= 26.5, 42.9, 124.8, 126.7, 128.7, 129.0, 130.5, 133.8, 134.0, 134.9, 166.9, 194.9.

5°/ *N*-methyl -3-(2-naphtyl)-3-oxopropanamide 1f

Yield: 93% ; a white solid; mp= 112-114°C ; ^{1}H NMR ($CDCl_3$) δ= 3.08-3.10 (d, 3H, J=4.8Hz), 4.29 (s, 2H), 7.48 (br, 1H) , 7.77-7.48 (m, 2H), 8.07-8.12 (m, 2H), 8.17-8.24 (m, 2H)), 8.75 (s,1H) ; ^{13}C NMR ($CDCl_3$) δ= 26.8, 45.6, 123.9, 127.5, 128.5, 129.3, 129.5, 130.2, 131.4, 132.7, 133.8, 136.3, 166.8, 196.5; MS (70 ev) : m /z= 227 ($M^{+\cdot}$, 19) ; 155 (100) ; 127 (72) ; 196 (5) .

6°/ *N*-methyl-3-oxo-hexanamide 1h
Yield: 88% ; a white solid; mp= 56-58°C ; ^{1}H NMR ($CDCl_3$) δ= 0.83-0.88 (t, 3H), 1.49-1.61 (m, 2H), 2.44-2.49 (t, 2H), 2.75-2.77 (d, 3H), 3.33 (s, 2H), 7.1(br, 1H); ^{13}C NMR ($CDCl_3$) δ= 13.5, 16.8, 26.2, 45.6, 48.2, 166.4, 207.0.

7°/ *N*-methyl-3-oxo-octadecanamide 1i
Yield: 89% ; a white solid; mp= 93-95°C ; ^{1}H NMR ($CDCl_3$) δ= 0.84-0.89 (m, 3H), 1.24 (m, 8H), 1.56 (m, 2H), 2.48-2.53 (t, 2H), 2.81-2.82 (d, 3H, J=4.8Hz), 3.39 (s, 2H), 7.1(br, 1H)); ^{13}C NMR ($CDCl_3$) δ= 14.1, 22.7, 23.4, 26.2, 29.0, 29.3, 29.4, 29.4, 29.6, 29.7, 31.9, 44.1, 48.4 166.2, 207.6.

Procedure B
1.1eq (4mL) of phenylacetylchloride and 2eq (4.5 mL) of pyridine has been added to a dichloromethane solution of Meldrum's acid (4g). The solution has been stirred under argon at 0°C for 1h and allowed to return to room temperature during 1h. The acyl Meldrum's acid has been isolated in a quantitative yield. A solution of this compound (1.2 eq) and benzylamine (1 eq, 2.7 mL) in anhydrous benzene (100 mL) has been refluxed for 4h. The solvent has been evaporated under reduced pressure and the residue obtained has been purified by column chromatography on silica gel [cyclohexane/ ethyl acetate: 80/20]

8°/ *N*-benzyl-3-oxo-3-(benzyl)propanamide 1d
Yield: 88%; a white solid; mp= 94-95°C ; ^{1}H NMR ($CDCl_3$) δ= 3.46 (s, 2H), 3.80 (s, 2H), 4.41-4.43 (d, 3H, J=5.7Hz), 5.6 (br, 1H) , 7.16-7.34 (m, 10H), ^{13}C NMR ($CDCl_3$) δ= 43.6, 47.9, 50.8, 127.5, 127.7, 128.6, 128.7, 129.0, 129.5, 132.8, 137.8, 165.3, 204.4 ; MS (70 eV) : m /z= 267 (M^+, 17) ; 106 (16) ; 91 (100) ; 65 (32).

Procedure C
This method consisted of heating the solution of nucleophile, methylacetoacetate in xylene on a hot plate. At approximately 120°C. The reaction was stopped once the solution reached the boiling point of xylene (ca. 10-15 min after boiling first noted).

9°/ 3-oxo- *N*-phenylbutanamide 1g
Yield: 83%; a white solid; mp= 83°C (lit.[21] mp= 84°C); ^{1}H NMR ($CDCl_3$) δ= 2.26 (s, 3H), 3.56 (s, 2H), 7.09-7.55 (m, 5H), 9.24 (br, 1H), ^{13}C NMR ($CDCl_3$) δ= 31.4, 50.5, 120.6, 125.0, 129.3, 137.9, 164.4, 205.3.

***In situ* preparation of dibromodiphosphine ruthenium (II) complexes** [$RuBr_2$((L*)]
(S)-SYNPHOS (7.5 mg, 0.012 mmol) and (Cod)Ru(2-methylallyl)$_2$ (3.2 mg, 0.01 mmol) have been placed in a 10 mL Schlenk tube and the vessel has been purged with argon. Anhydrous acetone ((2mL) degassed by cycles of vacuum /argon at room temperature) has been added. 0.125 mL of methanolic HBr solution (0.176 M, 2.2 mmol) has been added to this suspension and it bas been stirred during 30 mn at room temperature. A yellow solid precipitated. Subsequently, the solvent has been thoroughly evaporated under vacuum and the catalyst has been immediately used.

General hydrogenation procedure
A solution of the substrate *N*-methyl -3-oxo-3-phenylpropanamide (0.177 g, 1 mmol) has been diluted in degassed methanol (3 mL). This solution has been canulated into a 10 mL schlenk tube and degassed by 3 cycles of vacuum/argon. This mixture has been added to the Ru-catalyst (1% mol) in a glass vessel and placed under argon. The argon atmosphere has been replaced with hydrogen by 3 cycles of pressurizing. Hydrogenations have been run under the desired hydrogen pressure and temperature. The conversion rate has been determined by ^{1}H NMR analysis.

10°/ (R)-(+)-3-Hydroxy- *N*-methyl -3-phenylpropanamide 2a

Yield: 94% ; a white solid; mp= 125-126°C ; $[\alpha]_D$= +43(*c*1, $CHCl_3$) ; $[\alpha]_D$= +25.1(*c* 1, EtOH) ; IR (KBr disk) : ν= 3331(ν_{OH-NH}), 3111 (ν_{CH3}), 1645(ν_{CO}); ^{1}H NMR ($CDCl_3$) δ= 2.50-2.59 (m, 2H), 2.83-2.85 (d, 3H, J=4.8Hz), 4.18 (br, 1H), 5.09-5.16 (t, 1H, J=9Hz) ; 5.83 (br, 1H), 7.31-7.39 (m=5H) ; ^{13}C NMR ($CDCl_3$) δ= 26.3, 44.4, 70.7, 125.4, 127.7, 128.5, 152.4, 172.4; MS (70 eV) : m /z= 179 (M^+, 21); 73(100); 105(26) ; 58(24) ;43(25).

Enantiomers were well separated on the chiracel OJ column (The mobile phase used was hexane/isopropanol: 90/10). The retention time of major isomer was (8.302 mn) and the retention time of minor isomer was (10.447 mn)

11°/ (R)- (+)-3-(4-fluorophenyl)-3-Hydroxy- *N*-methylpropanamide 2b

Yield: 92% ; a white solid; mp= 124-126°C ; $[\alpha]_D$= +46(*c* 1.2, $CHCl_3$) ; IR (KBr disk) : ν= 3237-3321(ν_{OH-NH}), 2936 (ν_{CH3}), 1638(ν_{CO});^{1}H NMR ($CDCl_3$) δ= 2.42-2.59 (m, 2H), 2.77-2.79 (d, 3H, J= 4.5Hz), 4.6 (br, 1H), 5.03-5.06 (m, 1H), 6.14(br, 1H), 6.98-7.04 (m, 2H), 7.28-7.33 (m, 2H) ;^{13}C NMR ($CDCl_3$) δ= 26.5, 44.9, 70.6, 115.5, 115.8, 127.5, 127.7, 139.2, 139.3, 160.9, 164.1 , 172.8; MS (70 eV) : m /z= 197 (M^+, 35); 123(30) ; 97(48) ;73(100).

Enantiomers were well separated on the chiracel OJ column (The mobile phase used was hexane/isopropanol: 80/20). The retention time of minor isomer was (7.016 mn) and the retention time of major isomer was (8.722 mn)

12°/ (S)- (-)-3-Hydroxy- *N*-methyl -3-(4-methylphenyl)propanamide 2c

Yield: 93% ; a white solid; mp= 117-118°C ; $[\alpha]_D$= -34(*c* 1, $CHCl_3$) ; IR (KBr disk) : ν= 3230-3327(ν_{OH-NH}), 2931 (ν_{CH3}), 1653(ν_{CO}); ^{1}H NMR ($CDCl_3$) δ= 2.31 (s, 3H), 2.47-2.53 (m, 2H), 2.74-2.76 (d, 3H, J= 4.8Hz), 4.43(br, 1H), 4.98-5.02 (m, 1H), 6.27 (br, 1H), 7.10-7.13 (d, 2H, J= 8.1Hz), 7.19-7.21 (d, 2H, J= 8.1Hz), ; ^{13}C NMR ($CDCl_3$) δ= 21.1, 26.2, 44.6, 70.7, 125.5, 129.2, 137.3, 140.2, 172.7; MS (70 eV): m /z= 193 (M^+, 42); 176(39); 119(28) ; 91(43); 73(100).

Enantiomers were well separated on the chiracel OJ column (The mobile phase used was hexane/isopropanol: 80/20). The retention time of minor isomer was (7.854 mn) and the retention time of major isomer was (10.193 mn)

The X-ray crystallographic study of **2c** was carried out on a CAD4 Enraf-Nonius diffractometer (Mo Kα). Data were collected at 293 K in the range 1-28° and this, gave a total of 2377 reflections, yielding 2250 independent reflections (Rint =0.0254). The crystal structure carried out with a direct method from the SHELXS-97[22]permitted to locate the benzene group. The other non-hydrogen atoms were rapidly located after subsequent cycles of refinement and difference Fourier systhesis using the program SHELXL-97[22]. After anisotropic least-squares refinement, R was 5.76% and the difference map calculated at this point revealed the positions of all H atoms. In the final least-squares refinement of atomic parameters with isotropic thermal factors of the H atoms, R decreased to 3.94% (R_w= 10.57%). The experimental conditions of data collections, strategy followed for the structure determination, and final results are given in table II. Main geometrical features, bond distances and angles are reported in table III.

Table II: Crystal data and structure refinement for $C_{11}H_{15}N_1O_2$.

Empirical formula	$C_{11}H_{15}N_1O_2$
Formula weight	193.24
Temperature	293(2) K
Wave length	0.71073 Å
Crystal system, space group	Monoclinic, $P2_1$
Unit cell dimensions	a=10.0780(10) Å, α = 90°.
	b=4.8516(6) Å, β= 100.87(3)°.
	c=11.0595(10) Å, γ = 90°.
Volume	531.05(10) $Å^3$
Z, Calculated densty	2, 1.208 Mg / m^3
Absorption coefficient	0.083 mm^{-1}
F(000)	208
Crystal size	0.62 x 0.36 x 0.18 mm
Theta range for data collection	1.88 to 27.99 deg.
Limiting indicies	-13<=h<=13, -6<=k<=6, 0<=l<=0
Reflations collected / unique	2377 / 2250 [R(int) = 0.0254]
Absorption correction	Empirical (DIFABS)
Max. and min. transmission	0.9852 and 0.9503
Refinement method	Full-Matrix least –squares on F^2
Data / restraints / parameters	2250 / 1 / 187
Googness-of-fit on F^2	0.966
Final R indices [I>2 sigma (I)]	R1 = 0.0394, wR2 = 0.1057
R indices (all data)	R1 = 0.0552, wR2 = 0.1186
Absolute structure parameter	1.2(12)
Largest diff. peak and hole	0.1044 and -0.200 e $Å^{-3}$

Table III: Bond lengths [Å] and angles [deg] for $C_{11}H_{15}N_1O_2$.

O(1)-C(7)	1.4295(19)
C(7)-C(1)	1.510(2)
C(7)-C(8)	1.523(2)
C(9)-O(2)	1.235(2)
C(9)-N	1.331(2)
C(9)-C(8)	1.507(2)
N-C(10)	1.449(3)
C(4)-C(5)	1.384(3)
C(4)-C(3)	1.395(3)
C(4)-C(11)	1.510(3)
C(1)-C(2)	1.397(3)
C(1)-C(6)	1.396(2)
C(5)-C(6)	1.385(3)
C(2)-C(3)	1.384(3)
O(1)-C(7)-C(1)	112.87(15)
O(1)-C(7)-C(8)	110.84(14)
C(1)-C(7)-C(8)	110.02(12)
O(2)-C(9)-N	122.27(18)
O(2)-C(9)-C(8)	121.84(16)
N-C(9)-C(8)	115.85(14)
C(9)-N-C(10)	121.98(17)
C(5)-C(4)-C(3)	117.96(18)
C(5)-C(4)-C(11)	121.71(19)
C(3)-C(4)-C(11)	120.3(2)
C(2)-C(1)-C(6)	117.35(17)

13°/ (R)-3-Hydroxy-3- *N*-methyl -(1-naphthyl)-propanamide 2e

Yield: 94% ; a white solid; mp= 134-136°C ; $[\alpha]_D$= +16 (*c* 1, $CHCl_3$) ; IR (KBr disk) : ν= 3325-3300(ν_{OH-NH}), 3059 (ν_{CH3}), 1647(ν_{CO});^{1}H NMR ($CDCl_3$) δ= 2.52-2.71 (m, 2H), 2.76-2.77 (d, 3H , J=4.8Hz), 4.22 (br, 1H), 5.80-5.84(m, 1H), 5.66 (br, 1H), 7. 38-7.48 (m, 3H), 7.76-7.97 (m, 4H); ^{13}C NMR ($CDCl_3$) δ= 21.1, 26.2, 44.6, 70.7, 125.5, 129.1, 137.3, 140.2, 172.7; MS (70 eV): m /z= 229 (M^+, 60); 128(100); 211(54); 181(77) ;58(21)
Enantiomers were well separated on the chiracel OD-H column (The mobile phase used was hexane/isopropanol: 90/10). The retention time of minor isomer was (18.743 mn) and the retention time of major isomer was (21.246 mn)

14°/ (R)-3-Hydroxy-3- *N*-methyl -(2-naphthyl)-propanamide 2f
Yield: 92%; a white solid; mp= 122-124°C; ^{1}H NMR ($CDCl_3$) δ= 2.54-2.56 (d, 2H, J= 3.9Hz), 2.72-2.74 (d, 3H, J=4.8Hz), 4.48 (br, 1H), 5.16-5.20(m, 1H), 5.97 (br, 1H), 7. 36-7.45 (m, 3H), 7.74-7.78 (m, 4H); ^{13}C NMR ($CDCl_3$) δ= 26.6, 44.8, 71.3, 124.0, 124.6, 126.3, 126.6, 128.0, 128.3, 128.7, 133.3, 133.6, 140.8, 172.8; MS (70 eV): m /z= 229 (M^+, 22); 128(60); 73(100) ; 155(19); 212(5); 58(20).
Enantiomers were well separated on the chiracel OD-H column (The mobile phase used was hexane/isopropanol: 90/10). The retention time of minor isomer was (15.716 mn) and the retention time of major isomer was (17.120 mn)

15°/ (S)-*N*-benzyl-3- benzyl-3-bydroxypropanamide 2d
Yield: 91% ; a white solid; mp= 102-104°C ; $[\alpha]_D$= +16 (*c* 1, $CHCl_3$) ;^{1}H NMR ($CDCl_3$) δ= 2.18-2.36 (dd, 1H, J= 8.7Hz , J=15.3Hz), 2.64-2.82 (dd, 1H, J=8.7 , 15.3Hz), 3.5 (br, 1H), 4.18-4.27(m, 1H), 4.33-4.36 (d, 2H, J=3.6Hz), 6.30(br, 1H), 7.16-7.32 (m, 10H); ^{13}C NMR ($CDCl_3$) δ= 41.6, 43.3, 43.4, 69.6, 126.6, 127.5, 127.7, 128.5, 129.4, 137.6, 137.9, 171.8; MS (70 eV): m /z= 269 (MH^+, 40); 178(43); 91(100)
Enantiomers were well separated on the chiracel OD-H column (The mobile phase used was hexane/isopropanol: 90/10). The retention time of minor isomer was (14.438 mn) and the retention time of major isomer was (18.001 mn)

16°/ (*S*)-(+)- 3-Hydroxy-*N*-phenylbutanamide 2g
Yield: 94% ; a white solid; mp= 105°C; ^{1}H NMR ($CDCl_3$) δ= 1.12-1.14 (d, 3H), 2.31-2.36 (m, 2H), 4.11-4.17 (m, 1H), 6.26-7.34 (m, 5H), 7.54 (br, 1H)); ^{13}C NMR ($CDCl_3$) δ= 24.0, 45.6, 65.0, 121.6, 129.0, 124.4, 138.5, 173.0.

17°/ (*S*)-*N*-methyl-3-hydroxyhexanamide 2h
Yield: 92%; a white solid; mp= 66-68°C; ^{1}H NMR ($CDCl_3$) δ= 0.80-1.00 (t, 3H), 1.41-1.55 (m, 4H), 2.21-2.39 (m, 2H), 2.82-2.83 (d, 3H), 3.97-4.03 (m, 1H), 5.193(br, 1H);
^{13}C NMR ($CDCl_3$) δ=13.9, 18.6, 26.1, 39.0, 42.3, 68.3, 173.1
Enantiomers were well separated on the chiracel OD-H column (The mobile phase used was hexane/isopropanol: 90/10). The retention time of minor isomer was (18.318 mn) and the retention time of major isomer was (20.714 mn)

18°/ (*S*)-*N*-methyl-3-hydroxyoctadecanamide 2i
Yield: 94%; a white solid; mp= 102-104°C; ^{1}H NMR ($CDCl_3$) δ= 1.44-1.77 (m, 31H), 2.45-2.53 (m, 2H), 3.02-3.03 (d, 3H), 3.70-3.80 (br, 1H)
Enantiomers were well separated on the chiracel OD-H column (The mobile phase used was hexane/isopropanol: 92/02). The retention time of major isomer was (10.986 mn) and the retention time of minor isomer was (12.544 mn)

Acknowledgments

We are grateful to the CMCU (Comité Mixte Franco-Tunisien pour la Coopération Universitaire), the DGRSRT (Direction Générale de la Recherche Scientifique et de la Rénovation Technologique) for grants to « Laboratoire de Synthèse Organique Asymétrique et Catalyse Homogène : 01 UR 12 01». We wish also to thank Mr. T. Guerfel<<Service Commun pour la diffraction RX>> from the Faculty of Sciences of Monastir for the XR determination of the structure of (*S*)-3-Hydroxy-3-(4-methylphenyl)-*N*-methylpropanamide.

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