Ru-SYNPHOS® and Ru-DIFLUORPHOS®: Highly Efficient Catalysts for Practical Preparation of β-Hydroxy Amides

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Received 22 July 2005

Abstract: Ru-SYNPHOS® and Ru-DIFLUORPHOS® catalysts were efficiently used for the synthesis of a wide variety of chiral β-hydroxy amides via asymmetric hydrogenation of the corresponding β-keto amides.

Key words: catalysts, hydrogenation, enantioselectivity, ruthenium

Chiral β-hydroxy amides **1** are useful building blocks for the synthesis of biologically active compounds.[1] Examples include (*R*)-fluoxetine (**2**)[2] used as antidepressant, *N*′-(3-hydroxy-12-methyltridecanoyl)nornicotine (**3**)[3] as selective toxic agent against the larvae of *Manduca sexta* and BO-2727 (**4**)[4] having antimicrobial activity (Figure 1). Although the synthetic utility of this family of compound is well established, there are only few efficient methods for the enantioselective synthesis of such intermediates. Efficient synthesis were reported based on regioselective epoxide ring-opening reactions.[2a,5]

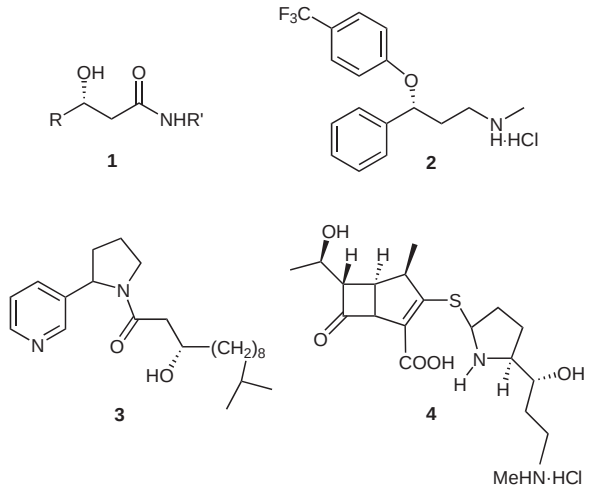


Figure 1

The direct asymmetric reduction of β-keto amides is a convenient route to synthesize optically active β-hydroxy amides **1**. Enzymatic reduction of β-keto amides with baker's yeast[6,7] led to 56–98% ee values. Because the scope of baker's yeast was limited, the biocatalytic reduction of 3-oxo-3-phenylpropanamide and 3-oxobutanamide derivatives was reported in good yields and enantioselectivities ranging from 43% to 98%.[8] Asymmetric reduction of acetoacetanilide with a $NaBH_4$-L-tartaric acid system was reported.[9] An alternative approach to chiral β-hydroxy amides was the homogeneous catalytic asymmetric hydrogenation of β-keto amides. To the best of our knowledge, most of these examples involved Ru-BINAP as chiral catalysts with a limited number of substrates. Noyori et al. reported one example of quantitative Ru-BINAP-catalyzed hydrogenation reaction of *N*,*N*-dimethyl 2-oxo-butanamide at 63 atm for 86 hours with 96% ee.[10] The Ru-BINAP-promoted hydrogenation of alkyl-substituted β-ketoamides was achieved with good level of enantio- and diastereoselectivites.[11,12] The synthesis of the chiral fluoxetine intermediate **1** (R = Ph, R′ = Me) was described in a moderate 50% yield and >99.9% ee after repeated recrystallization by using {$RuCl_2$[(*S*)-BINAP]} at 200 psi and 100 °C for 18 hours.[13] Thus, the development of an efficient and practical route towards various chiral β-hydroxy amides could be useful since they are precursors of optically pure 1,3-aminoalcohols which have found a widespread use in organic chemistry as chiral units of synthetic utility.[14]

In previous communications, we have described the synthesis of new atropisomeric diphosphines (Figure 2) named SYNPHOS[15] and DIFLUORPHOS.[16]

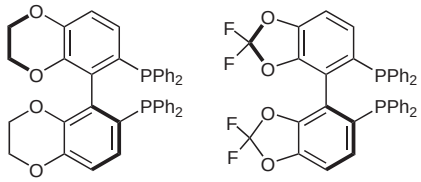
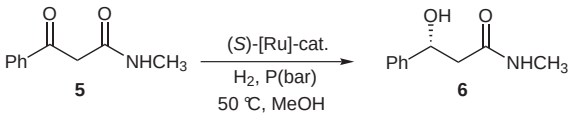


Figure 2

SYNLETT 2005, No. 16, pp 2478–2482
Advanced online publication: 21.09.2005
DOI: 10.1055/s-2005-917089; Art ID: G23405ST

Our studies have demonstrated both their relevant steric and electronic properties and their catalytic performance in ruthenium-promoted hydrogenation reactions.[15,16,17c–e] As part as our continuing interest in the homogeneous ruthenium-promoted hydrogenation reactions,[17] we wish to report in this paper a new application of chiral Ru-SYNPHOS and Ru-DIFLUORPHOS catalysts for the synthesis of a wide range of β-hydroxy amides with high optical purity.

We first examined the Ru-SYNPHOS-promoted hydrogenation reaction of benzoylacetamide **5** as representative substrate (Scheme 1). The catalytic tests were performed in methanol at 50 °C under 5–10 bar of hydrogen pressure with a substrate/catalyst ratio (S/C) of 100 (Table 1). Preliminary study was carried out under 5 bar of hydrogen pressure for 10 hours by using the in situ generated {$RuBr_2$[(*S*)-SYNPHOS]} prepared from a mixture of (COD)Ru(2-methylallyl)$_2$ and the diphosphine by addition of 2.2 equivalents of HBr according to our convenient procedure.[18] The β-hydroxy amide **6** was obtained in 76% yield and 96% ee (entry 1). By increasing the pressure to 10 bar, the reaction proceeded faster and with excellent 91% yield and 96% ee (entry 2). When BINAP was used as ligand, a comparable yield and ee (90% yield, 94% ee) was obtained but the reaction time increased to 15 hours (entry 3). Fully comparable results were achieved in 8 hours by using {$RuBr_2$[(*S*)-MeO-BIPHEP]} and {$RuBr_2$[(*S*)-DIFLUORPHOS]} under analogous conditions (entries 4 and 5, respectively: 90% and 94% yield, 96% and 93% ee).



Scheme 1

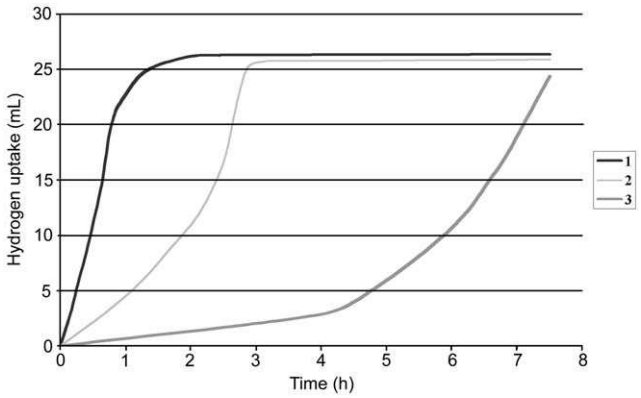


Figure 3 Hydrogen uptake vs. time for the Ru-SYNPHOS asymmetric hydrogenation of **5**. (1) {(RuCl[(*R*)-SYNPHOS)]$_2$ (μ-Cl)$_3$}[NH_2Me_2], ee = 99% (2) {$RuBr_2$[(*R*)-SYNPHOS]}, ee = 96% (3) {Ru(*p*-cymene)[(*S*)-SYNPHOS]Cl}Cl, ee = 87%

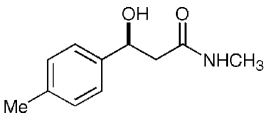
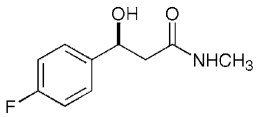
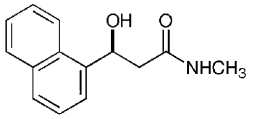
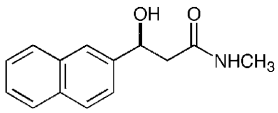
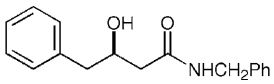
Next, a comparative study was carried out between some Ru-SYNPHOS catalysts such as {(RuCl[(*R*)-SYNPHOS)]$_2$(μ-Cl)$_3$}[NH_2Me_2] and {Ru(*p*-cymene)[(*S*)-SYNPHOS]Cl}Cl. Results in Figure 3 are issued from a parallel screening using the TOP INDUSTRIE parallel hydrogenation system (TOP 1 590 000).[19] This commercially available equipment aims at screening several hydrogenation reactions on small to large scale with independent control of temperature and pressure. Individual monitoring of hydrogen uptake led to the kinetic profiles of each reaction. The parallel catalytic tests have been run under the same reaction conditions (entries 2, 6, 7, 10 bar, 50 °C, S/C = 100). This graph allowed determining the best reaction time for the Ru-SYNPHOS catalysts. When comparing the catalytic activities of the different Ru-SYNPHOS catalysts (Figure 3), we observed that {(RuCl[(*R*)-SYNPHOS)]$_2$ (μ-Cl)$_3$}[NH_2Me_2] catalyst enhanced exceedingly the hydrogenation reaction rates of **5** (curve 1) compared to both {$RuBr_2$[(*R*)-SYNPHOS]} (curve 2) and {Ru(*p*-cymene)[(*S*)-SYNPHOS]Cl}Cl (curve 3).

Table 1 Optimization of the Asymmetric Hydrogenation of **5** in Methanol

Entry	Ru catalyst[a]	P (bar)	Time (h)	Yield (%)[b]	ee (%)[c]
1	{$RuBr_2$[(*S*)-SYNPHOS]}	5	10	76	96 (*R*)
2	{$RuBr_2$[(*S*)-SYNPHOS]}	10	3	91	96 (*R*)
3	{$RuBr_2$[(*R*)-BINAP)}	10	15	90	94 (*S*)
4	{$RuBr_2$[(*S*)-MeO-BIPHEP]}	10	8	90	96 (*R*)
5	{$RuBr_2$[(*S*)-DIFLUORPHOS]}	10	8	94	93 (*R*)
6	{(RuCl[(*R*)-SYNPHOS)]$_2$ (μ-Cl)$_3$}[NH_2Me_2]	10	2	95	99 (*S*)
7	{Ru(*p*-cymene)[(*S*)-SYNPHOS]Cl}Cl	10	10	75	87 (*R*)
8	{(RuCl[(*R*)-SYNPHOS)]$_2$ (μ-Cl)$_3$}[NH_2Me_2]	10	2	92[d]	98 (*S*)

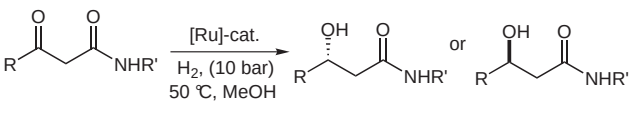
[a] Reaction carried out with S/C = 100.
[b] Isolated yield after flash chromatography.
[c] The ee were determined by HPLC analysis.
[d] Reaction was conducted on 1.5 g scale.

Table 2 Asymmetric Hydrogenation of β-Keto Amides **7**–**11** with Ru-SYNPHOS and Ru-DIFLUORPHOS Catalysts

Entry	Substrate	Ru catalyst[a]	Time (h)	Yield (%)[c]	Product	ee (conf.) (%)[d]
1	**7**	{(RuCl[(*R*)-SYNPHOS)]$_2$ (μ-Cl)$_3$}[NH_2Me_2]	19[b]	93		99 (*S*)
2	**7**	{$RuBr_2$[(*S*)-SYNPHOS]}	19[b]	92	**15**	99 (*R*)
3	**7**	{$RuBr_2$[(*S*)-DIFLUORPHOS]}	19[b]	91	**15**	94 (*R*)
4	**8**	{(RuCl[(*R*)-SYNPHOS)]$_2$ (μ-Cl)$_3$}[NH_2Me_2]	1	92		>99 (*S*)
5	**8**	{$RuBr_2$[(*S*)-SYNPHOS]}	1	91	**16**	>99 (*R*)
6	**8**	{$RuBr_2$[(*R*)-DIFLUORPHOS]}	1.5	92	**16**	>99 (*S*)
7	**9**	{(RuCl[(*R*)-SYNPHOS)]$_2$ (μ-Cl)$_3$}[NH_2Me_2]	2	93		>99 (*S*)
8	**9**	{$RuBr_2$[(*R*)-SYNPHOS]}	1	91	**17**	>99 (*S*)
9	**9**	{$RuBr_2$[(*R*)-DIFLUORPHOS]}	5	70	**17**	>99 (*S*)
10	**9**	{$RuBr_2$[(*S*)-DIFLUORPHOS]}	5	80	**17**	>99 (*R*)
11	**10**	{(RuCl[(*R*)-SYNPHOS)]$_2$ (μ-Cl)$_3$}[NH_2Me_2]	2	91		93 (*S*)
12	**10**	{$RuBr_2$[(*S*)-SYNPHOS]}	5	92	**18**	89 (*R*)
13	**11**	{(RuCl[(*R*)-SYNPHOS)]$_2$ (μ-Cl)$_3$}[NH_2Me_2]	19[a]	90		95 (*R*)
14	**11**	{$RuBr_2$[(*R*)-SYNPHOS]}	5	89	**19**	97 (*R*)
15	**11**	{$RuBr_2$[(*R*)-DIFLUORPHOS]}	5	91	**19**	97 (*R*)

[a] Reaction carried out with S/C = 100.
[b] Reaction time not optimized.
[c] Isolated yields after flash chromatography.
[d] The ee were determined by HPLC analysis using Chiralcel OD-H or Chiralcel OJ column.

Thus, this study was extended to a series of β-keto amides prepared according to the literature.[20] The range of β-keto amides **7**–**11** is illustrated in Scheme 2. The screening tests were carried out on a 1 mmol scale in methanol under 10 bar hydrogen pressure at 50 °C by using 1 mol% of the Ru-SYNPHOS and Ru-DIFLUORPHOS catalysts (Table 2). In all cases, complete conversions were achieved. As illustrated in Table 2, all hydrogenations exhibited both excellent level of enantioselectivities, yields and high substrate generality. In all cases, both {(RuCl[(*R*)-SYNPHOS)]$_2$ (μ-Cl)$_3$}[NH_2Me_2] and {$RuBr_2$[(*R*)-SYNPHOS]} catalysts have been engaged in the ruthenium-promoted hydrogenation of aromatic β-keto amides **7**–**11** (Table 2) leading to excellent yields up to 93% for the *para*-substituted compounds **7** and **8** with no influence of the *para*-substituents (*p*-Me–Ph, entries 1, 2 or *p*-F–Ph, entries 4 and 5). Interestingly, the more hindered substrates such as **9** and **10** were hydrogenated with ee in a range from 89% to 99% (entries 7, 8, 11, 12). We were pleased to find that homogeneous system based on Ru-DIFLUORPHOS gave good results with yields up to 90% and ee in a range from 94% to >99% (entries 3, 6, 9, 10, 15).

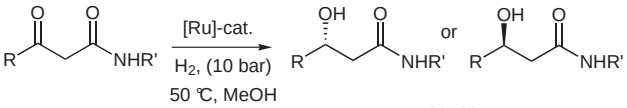


15–**19**

7 R = *p*-Me-C_6H_4, R' = Me
8 R = *p*-F-C_6H_4, R' = Me
9 R = 1-Naphth, R' = Me
10 R = 2-Naphth, R' = Me
11 R = CH_2Ph, R' = CH_2Ph

Scheme 2

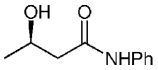
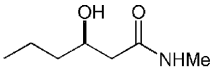
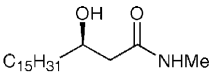
To extend the scope of this versatile methodology with conditions established for the catalytic hydrogenation of β-aryl-substituted keto amides, this procedure was applied to the hydrogenation of β-alkyl-substituted keto amides **12**–**14** (Scheme 3, Table 3). Once again, essentially quantitative conversions to enantiomerically enriched β-hydroxy amides **20**–**22** (entries 1–9) were observed under the same catalytic conditions. When SYNPHOS was used as chiral ligand, the hydrogenation reactions were performed again with excellent enantiofacial discrimination affording the corresponding enantiopure alcohols **21**–**22** (Table 3, entries 4, 5, 7, 8: ee >99%). Only one enantiomer was detected by HPLC analysis. When these transformations were repeated by using DIFLUORPHOS ligand, slightly lower ee were obtained together with very good yields (entries 3, 6, 9: 96–99% ee, 90–93% yields).



12 R = Me, R' = Ph
13 R = *n*-Pr, R' = Me
14 R = $C_{15}H_{31}$, R' = Me

Scheme 3

Table 3 Asymmetric Hydrogenation of β-Keto Amides **12**–**14** with Ru-SYNPHOS and Ru-DIFLUORPHOS Catalysts

Entry	Substrate	Ru-catalyst[a]	Time (h)	Yield (%)[b]	Product	ee (conf.) (%)[d]
1	**12**	{(RuCl[(*R*)-SYNPHOS)]$_2$ (μ-Cl)$_3$}[NH_2Me_2]	1	92		99 (*R*)[c]
2	**12**	{(RuCl[(*S*)-SYNPHOS)]$_2$ (μ-Cl)$_3$}[NH_2Me_2]	1	94	**20**	99 (*S*)[c]
3	**12**	{$RuBr_2$[(*R*)-DIFLUORPHOS]}	4	90	**20**	96 (*R*)[c]
4	**13**	{(RuCl[(*R*)-SYNPHOS)]$_2$ (μ-Cl)$_3$}[NH_2Me_2]	0.5	91		>99 (*R*)
5	**13**	{(RuCl[(*S*)-SYNPHOS)]$_2$ (μ-Cl)$_3$}[NH_2Me_2]	0.5	92	**21**	>99 (*S*)
6	**13**	{$RuBr_2$[(*R*)-DIFLUORPHOS]}	5	90	**21**	99 (*R*)
7	**14**	{(RuCl[(*R*)-SYNPHOS)]$_2$ (μ-Cl)$_3$}[NH_2Me_2]	1	92		>99 (*R*)
8	**14**	{(RuCl[(*S*)-SYNPHOS)]$_2$ (μ-Cl)$_3$}[NH_2Me_2]	1	94	**22**	>99 (*S*)
9	**14**	{$RuBr_2$[(*R*)-DIFLUORPHOS]}	4	93	**22**	96 (*R*)

[a] Reaction carried with S/C = 100.
[b] Isolated yields after flash chromatography.
[c] The ee were determined by ^1H NMR (400 MHz) of (+)-MTPA ester derivatives.
[d] The ee were determined by HPLC analysis using Chiralcel OD-H or Chiralcel OJ column.

The absolute configurations of the chiral β-hydroxy amides **6** and **21** were assigned from $[\alpha]_D$ value by comparison with known compounds.[8,12a,13] Concerning the β-keto amides **7**–**11**, we assumed that their hydrogenation follows the same stereochemical outcome as above according to the stereochemical model proposed for the hydrogenation reaction of carbonyl derivatives with ruthenium-arylphosphine catalysts.[17,21]

In conclusion, we outlined the development of a general route that provides access to a wide variety of chiral β-hydroxy amides by using the ruthenium-promoted hydrogenation of corresponding β-keto amides. In this work, we have demonstrated that the SYNPHOS and DIFLUORPHOS ligands can be efficiently used in these transformations. This procedure is simple to perform[22,23] and allows the convenient preparation of both enantiomers with high level of enantioselectivites enabling the synthesis of natural products and analogues of biological interest.

Acknowledgment

We would like to thank the CMCU (Comité Mixte Franco-Tunisien pour la Coopération Universitaire) for financial support.

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(23) **General Hydrogenation Procedure.**
(*S*)-SYNPHOS (7.5 mg, 1.2×10^{-2} mmol) and (COD)Ru(2-methylallyl)$_2$ (3.2 mg, 1.0×10^{-2} mmol) were placed in a 5 mL flask and 2 mL of anhyd acetone were added. A methanolic solution of HBr (0.122 μL, 0.18 M) was added to the resulting suspension and the reaction mixture was stirred at r.t. for about 30 min. The solvent was removed under vacuum. The yellow solid residue was used as catalyst for the hydrogenation reaction. Then, MeOH (4 mL), acetoacetanilide (**5**, 177 mg, 1 mmol) and the catalyst were placed under argon in the TOP INDUSTRIE parallel hydrogenation system. The autoclave was pressurized to an initial pressure of 10 bar of hydrogen and the reaction was allowed to proceed at 50 °C for 2 h. The crude reaction mixture was purified by silica gel chromatography (cyclohexane–EtOAc, 50:50) to afford 163 mg of (*R*)-**6** as a white solid (91%). Mp 125–126 °C; $[\alpha]_D$ +43 (*c* 1, $CHCl_3$); $[\alpha]_D$ +29 (*c* 1, CH_3OH). IR (KBr disk): 3331 (ν_{OH-NH}), 3111 (ν_{CH3}), 1645 (ν_{CO}) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.50–2.59 (m, 2 H), 2.84 (d, *J* = 4.8 Hz, 3 H), 4.18 (br, 1 H), 5.09–5.16 (dd, *J* = 5.0, 7.6 Hz, 1 H), 5.83 (br, 1 H), 7.31–7.39 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ = 26.0, 44.4, 70.7, 125.4, 142.9, 152.4, 172.4. MS (70 eV): *m/z* (%) = 179 (21) [M^+], 73 (100), 105 (26), 58 (24), 43 (25).