Optically Active Amine Derivatives: Ruthenium-Catalyzed Enantioselective Hydrogenation of Enamides

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Abstract: Enamides have first been prepared by reaction of 5-methoxy-3-chromanone and 2-tetralone with primary amides under acidic conditions. The enantioselectivities observed in the asymmetric hydrogenation of these enamides using ruthenium catalysts strongly depended on both the starting ketone and the nature of the amide group.

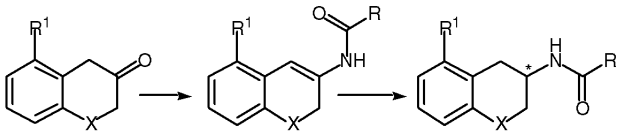
Key words: ketone, enamide, enantioselective hydrogenation, ruthenium catalyst

Optically active amine derivatives constitute a class of key intermediates towards human health products and may be used as efficient ligands for asymmetric catalysis.[1] Up to now, one of the most direct routes for the access to these compounds appears to result from the enantioselective catalytic hydrogenation of enamides. Since the first example reported by Kagan and coworkers using rhodium-diop catalyst precursor,[2] excellent enantioselectivities were recently reached in the presence of ruthenium-binap[3,4] and rhodium-duphos or rhodium-pennphos[5] precatalysts.

The transformation of a ketone into an enamide is an efficient way to generate a prochiral amine derivative containing a chelating functional group able to orientate the enantioselective hydrogenation. According to this strategy, Tschaen and coworkers reported the synthesis of several enamides by direct condensation of amides with a ketone during the course of asymmetric synthesis of MK-0499.[4] More recently, Burk and coworkers[5a] have reported a two-step method for synthesis of acetyl enamides starting from cyclic and acyclic ketones *via* acylation on nitrogen of oximes using acetic anhydride in the presence of iron powder and acetic acid.

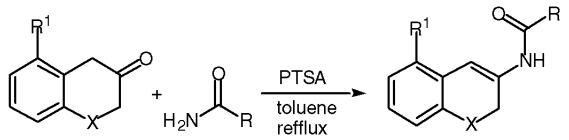
Among optically active amines, 3-aminochromans and 2-aminotetralins are of great interest, because they are present in biologically active compounds such as (+)-S 20499[6], MK-0499[4] and SR58611A.[7] This provided impetus to study the catalytic hydrogenation of chromanone and tetralone derivatives to obtain precursors of these two amines.

We now report:
i) an efficient preparation of various enamides from 5-methoxy-3-chromanone and 2-tetralone, and
ii) their enantioselective hydrogenation in the presence of optically active ruthenium catalysts into optically active amides (Scheme 1).



Scheme 1

The enamides were directly obtained from the non activated ketones **1** and **2** by direct reaction with primary amides under acidic conditions (Scheme 2).



1 R^1= OMe, X= O

2 R^1= H, X= CH_2

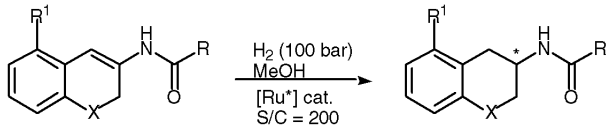
X= O, R^1= OMe:
3 (R= Me, 80%), **4** (R= Ph,52%)
X= CH_2, R^1= H:
5 (R= Me, 80%), **6** (R= CH_2Cl ,75%),
7 (R= Et, 98%), **8** (R= Ph, 80%)

Scheme 2

The enamides **3** and **4** were thus obtained by treatment of 10 mmol of the 5-methoxy-3-chromanone **1** with 25 mmol of amide in the presence of 1 mmol of paratoluenesulfonic acid (PTSA) (10 mol% with respect to the ketone) in refluxing toluene in a Dean-Stark apparatus for 20 h. The reaction mixture was then washed with water, dried over $MgSO_4$ and evaporated to dryness. The pure enamide **3** was obtain as a white solid in 80% yield after simple washing with pentane. Purification by chromatography over silica gel with an ether/pentane mixture as eluent gave the enamide **4** as a white solid in 52% yield. The commercially available 2-tetralone **2** (97% from Lancaster) was converted into the enamides **5**-**8** in 80, 75, 98, and 80% yield, respectively. In these cases the reaction had to be carried out under inert atmosphere in order to avoid degradation of the ketone. It is worth noting that, in the case of monochloroacetamide, the use of 5 equivalents of this amide and refluxing for 48 hours was necessary to obtain **6** in 75% yield. This is probably due the slight electron attracting effect of the chloromethyl group which leads to the deactivation of the amide moiety (in comparison to acetamide). The same effect probably explains

that, under similar conditions, no conversion into the desired product was obtained with trichloroacetamide.

The direct hydrogenation of the enamides was attempted in the presence of catalytic amounts of optically active ruthenium complexes containing the atropoisomeric Binap ligand: ((*R*)-Binap)$Ru(O_2CCF_3)_2$ **A** and $[NH_2Et_2][\{RuCl((S)\text{-Binap})\}_2(\mu\text{-}Cl)_3]$ **B**[8] (Scheme 3).[9]



X= O, R^1= OMe:
9 (R= Me), **10** (R= Ph)
X= CH_2, R^1= H:
11 (R= Me), **12** (R= CH_2Cl),
13 (R= Et), **14** (R= Ph)

Scheme 3

Table 1 Enantioselective Hydrogenation of Enamides **3-8**

Enamide	Catalyst	Temperature (°C)	Reaction time (h)	Yield [a] (%)	ee (%)
3	**A**	20	20	97	35
3	**B**	20	20	95	8
4	**A**	30	20	95	40
5	**A**	20	20	95	90
5	**A**	20	48	95[b]	90
5	**B**	20	20	94	80
6	**A**	60	20	95	64
6	**B**	60	20	94	47
6	**A**	20	20	95[c]	71
7	**A**	20	20	95	90
7	**B**	20	20	94	76
8	**A**	20	20	95	96
8	**B**	20	20	94	87

General conditions: hydrogen (100 bar), methanol (10 ml), substrate/catalyst = 200, total conversion of the enamide, (a) : isolated yield, (b) substrate/catalyst = 1000, (c) substrate/catalyst = 100, reaction times were not optimised. **A**: ((*R*)-Binap)$Ru(O_2CCF_3)_2$, **B**: $[NH_2Et_2][\{RuCl((S)\text{-Binap})\}_2(\mu\text{-}Cl)_3]$.

The enamides **3** and **4** obtained from the 5-methoxy 3-chromanone **1** were hydrogenated in methanol under 100 bar of hydrogen. The two enamides showed similar reactivities and complete conversion was obtained within 20 h under mild conditions at 20-30°C (Table 1).

During the hydrogenation of the ene acetamide **3**, an important difference in enantioselectivity was noticed when either **A** or **B** was used as catalyst (in the best case, 35% ee were obtained with catalyst **A**, whereas the precatalyst **B** led to 8% ee under similar conditions). Nevertheless, the utilization of ((*R*)-Binap))$Ru(O_2CCF_3)_2$ as catalyst for the hydrogenation of the enamides **3** and **4** afforded very modest enantioselectivities (35 and 40% ee, respectively).

Similarly, the 2-tetralone enamide derivatives **5-8** were hydrogenated under 100 bar of H_2 at 20-60°C in the presence of **A** or **B** as catalysts (Scheme 3). The results are summarized in the Table 1. In most cases the hydrogenation of 1 mmol of enamide went to completion at 20 °C within 20 h with a substrate/catalyst ratio of 200. The presence of the monochloroacetyl group in the enamide **6** led to a decrease of reactivity and only 50% of conversion was observed after 20 h at 20 °C. However, a reaction temperature of 60 °C or a substrate/catalyst ratio of 100 made possible the total conversion of 1 mmol of **6** in 20 h. Noyori and coworkers[3a] had previously reported that using a trifluoroacetyl group instead of an acetyl one led to a dramatic decrease of the reactivity in the asymmetric hydrogenation of the carbon-carbon double bond of an enamide substrate with the same type of ruthenium catalysts.

As noticed with the chromanone derivatives, we observed a difference in enantioselectivity between ((*R*)-Binap)$Ru(O_2CCF_3)_2$ **A** and $[NH_2Et_2][\{RuCl((S)\text{-Binap})\}_2(\mu\text{-}Cl)_3]$ **B** as catalysts, **A** always giving the best results. The presence of the chloro substituent on the amide group had a negative effect on the enantioselectivity of the hydrogenation. Whereas good ee's were obtained from acetyl (**5**) (90%), propionyl (**7**) (90%) and benzoyl (**8**) (96%) enamides at 20 °C with **A** as catalyst, only 71% ee was achieved from the substrate **6** under similar hydrogenation conditions. The overall effect of the exchange of an acetyl group into a monochloroacetyl one is a decrease of both reactivity and enantioselectivity. The best result obtained from the benzoyl enamide **8** (96% ee) was comparable to the enantioselectivities resulting from the hydrogenation of benzoyl enamides derived from 6- and 7-substituted 2-tetralone using ruthenium catalysts.[4,7]

During the course of hydrogenation of the acetyl enamide **5**, we tried to reduce the quantity of catalyst and were able to obtain complete conversion into the saturated substrate in 90% ee at 20 °C in 48 h with a substrate/catalyst ratio of 1000.

Starting from the same type of structure (fused 6-membered ring ketones with the carbonyl group in β-position with respect to the aromatic ring), enamides derived from the 5-methoxy-3-chromanone **1** and the 2-tetralone **2** gave quite different results in terms of enantioselectivity. The possible interaction, with the metal centre, of an ether oxygen atom, either from the pyran ring or the methoxy group on the aromatic ring or both of them in compounds **3** and **4**, leads to a dramatic decrease of the enantioselectivity during the hydrogenation reaction.

The direct hydrogenation of enamides containing an intracyclic C=C bond, in the presence of Binap-ruthenium catalysts leads to a complete conversion into saturated amides. Both reactivity and enantioselectivity strongly depend on the presence of an additional coordinating functionality on the substrate skeleton and on the nature of the amide. Excellent conversion and enantioselectivity with high substrate/catalyst ratio have been obtained from the 2-tetralone enamides.

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(9) Typical procedure for enantioselective hydrogenation of enamides **3-8**: 1 mmol of enamide and 0.005 mmol of ruthenium catalyst were placed in a 125 ml autoclave in 8 ml of methanol. After degassing with hydrogen, a pressure of 100 bar of hydrogen was applied. The autoclave was stirred mechanically during 20 to 60 h and the conversion was determined by ^{1}H NMR. After isolation of the hydrogenated amides by chromatography over silica gel with an ether/pentane mixture as eluent, the enantiomeric excesses were determined by HPLC with a chiral column (CHIRALCEL OD 25 cm).

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