Enantioselective Hydrogenation of the Tetrasubstituted C=C Bond of Enamides Catalyzed by a Ruthenium Catalyst Generated *in situ*

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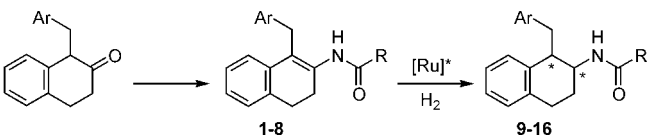
Abstract: The enantioselective hydrogenation of enamides bearing an endocyclic tetrasubstituted carbon-carbon double bond has been performed in the presence of ruthenium catalyst precursors prepared from Ru(cod)(methallyl)$_2$, Duphos, or BPE as optically active ligand and HBF_4. This promising catalytic system makes possible the selective *cis*-hydrogenation with satisfactory enantioselectivities (up to 72% ee) for this type of tetrasubstituted double bonds.

Keywords: enantioselectivity; homogeneous catalysis; hydrogenation; P ligands; ruthenium; tetrasubstituted enamides

Since the first example reported by Kagan,[1] enantioselective hydrogenation of enamides using chiral rhodium[2] and ruthenium[3] catalysts has developed to be a method of choice for access to optically active amine derivatives with high enantioselectivity. Whereas the hydrogenation of di- and trisubstituted C=C bonds is well documented, more hindered substrates are notoriously more difficult to reduce. Ito[4] and Burk[5] have reported the use of chiral rhodium complexes for the hydrogenation of β-disubstituted α-acetamidoacrylates. The enantioselective hydrogenation of the tetrasubstituted C=C bond of enamides is very difficult and only very recently, Zhang[6] has reported the hydrogenation of two tetrasubstituted enamides derived from 1-indanone and 1-tetralone using a rhodium-Pennphos precursor. But until now, no hydrogenation of the C=C bond of tetrasubstituted cyclic enamides catalyzed by ruthenium complexes has been described.

In this communication, we report the enantioselective hydrogenation of tetrasubstituted enamides derived from racemic 1-substituted-2-tetralones, into optically active amides possessing two stereogenic centers in the presence of an *in situ*-generated chiral ruthenium precursor (Scheme 1)



Scheme 1.

The direct transformation of a ketone into an enamide is a possible way to generate a prochiral amine derivative containing a chelating functional group capable of orientating the enantioselective hydrogenation. *para*-Toluenesulfonic acid, an active catalyst for the transformation of ketones into enamides,[7] was used for the direct transformation of non-activated 1-substituted-2-tetralones[8] into enamides by direct condensation with acetamide or propionamide (Table 1).[9] This simple method made possible the first direct synthesis of the tetrasubstituted enamides **1–8** in good yields from the corresponding non-activated ketones.[10]

Whereas the enantioselective hydrogenation of trisubstituted enamides derived from 2-tetralone can be performed in the presence of (Binap)Ru(O_2CCF_3)$_2$ or

Table 1. Synthesis of tetrasubstituted enamides **1–8**.[a]

Ar	R	Enamide	Yield (%)
phenyl	Me	**1**	75
(*o*,*o*)-dimethylphenyl	Me	**2**	65
(*o*,*o*)-dimethylphenyl	Et	**3**	65
p-methoxycarbonylphenyl	Et	**4**	83
o-methoxyphenyl	Et	**5**	80
o-chlorophenyl	Et	**6**	80
o-bromophenyl	Et	**7**	80
o-iodophenyl	Et	**8**	78

[a] General conditions: 1-substituted-2-tetralone (1 equiv.), primary amide (5 equiv.), PTSA (0.1 equiv.), toluene, reflux, Dean-Stark apparatus, 20 h.

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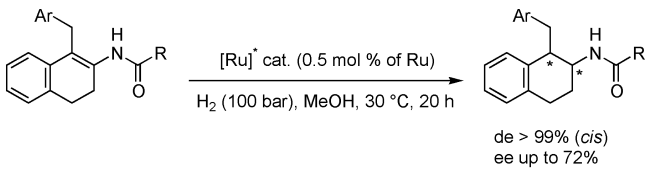
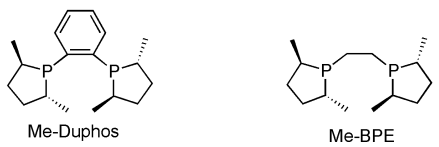
$[NH_2Et_2][\{(Binap)RuCl\}_2(\mu\text{-}Cl)_3]$ as efficient precatalysts,[7] with the more hindered substrates **1–8**, no reaction occurred after 20 hours at 30 °C in methanol under 100 bar of hydrogen. Moreover, the catalytic system $[Rh(COD)_2]BF_4$/Me-Duphos, efficient for the enantioselective hydrogenation of α-acetamidoacrylates, was not active in this case. The hydrogenation of the tetrasubstituted enamides **1–8** was successfully achieved using a ruthenium catalyst, generated *in situ* by protonation with two equivalents of tetrafluoroboric acid of a mixture of the ruthenium source (1,5-cyclooctadiene)Ru(methallyl)$_2$ and one equivalent of optically active diphosphine, the Me-Duphos or Me-BPE ligand (Scheme 2). This procedure is based on the easy displacement of the allyl groups upon protonation of the intermediate (diphosphine)Ru(methallyl)$_2$. It is related to the catalytic system generated *in situ* from an equimolar mixture of (COD)Ru(methallyl)$_2$, diphosphine, and $HBF_4 \cdot Et_2O$ in the presence of a catalytic amount of $BF_3 \cdot Et_2O$ described by Genêt, Rautenstrauch et al.[11] for the enantioselective hydrogenation of the intracyclic C=C bond of cyclic enones.

In all cases, the reaction of enamides **1–8**, with 0.5 mol % of ruthenium catalyst, went to completion at 30 °C within 20 hours and afforded amides as the single *cis*-diastereoisomers in good yields (95–98%) and ees up to 72% (Scheme 2). By comparison, the catalytic system generated *in situ* in the presence of $BF_3 \cdot Et_2O$[11] provided us only 25% of conversion under the same conditions.



[Ru]*: diphosphine / (COD)Ru(methallyl)$_2$ / HBF_4; molar ratio: 1/1/2
diphosphine: Me-Duphos, Me-BPE



Scheme 2.

The optically active amides **9–13** were prepared from the enamides **1–5**, and higher enantioselectivities were obtained with (*R,R*)-Me-Duphos as a ligand (Table 2; entries 3, 5, 7). The results clearly demonstrate the influence of the nature of the benzylic substituent on the enantioselectivity during the hydrogenation of these tetrasubstituted cyclic enamides, and the best results were obtained for the sterically hindered 1-[(*o*,*o*)-dimethylbenzyl]-2-aminotetraline derivatives **10** and **11** (72 and 68% ee, respectively) (Table 2). On the other hand, changing the amide group from acetamide to propionamide had no significant influence on the enantioselectivity of the hydrogenation (Table 2; entries 3, 5).

Table 2. Enantioselective hydrogenation of enamides **1–5**.[a]

Entry	Diphosphine	Enamide	Amide	ee (%)
1	(*R,R*)-Me-Duphos	**1**	**9**	52 (+)
2	(*S,S*)-Me-BPE	**2**	**10**	50 (–)
3	(*R,R*)-Me-Duphos	**2**	**10**	72 (+)
4	(*S,S*)-Me-BPE	**3**	**11**	60 (–)
5	(*R,R*)-Me-Duphos	**3**	**11**	68 (+)
6	(*S,S*)-Me-BPE	**4**	**12**	46 (–)
7	(*R,R*)-Me-Duphos	**4**	**12**	64 (+)
8	(*R,R*)-Me-Duphos	**5**	**13**	60 (+)

[a] Catalytic system: diphosphine/(COD)Ru(methallyl)$_2$/HBF_4 (molar ratio: 1/1/2), H_2 (100 bar), MeOH, 30 °C, 20 h, total conversion.

By contrast, from the *ortho*-halobenzyl-substituted enamides **6–8**, the best ees for the amides **14–16** were obtained with (*S,S*)-Me-BPE as a ligand (Figure 1). The nature of the halide plays a crucial role as the enantioselectivity increased with the size of the halogen atom in the *ortho* position. The *N*-propionyl-1-(*o*-chlorobenzyl)-2-aminotetraline **14** was obtained with 57% ee, whereas the hydrogenation of the iodo derivative led to **16** with 70% ee. Under similar conditions, in MeOH at 30 °C under 100 bar of hydrogen pressure, the use of the (*R,R*)-Me-Duphos ligand led to (+)-**14**, (+)-**15**, and (+)-**16** in 56, 44, and 2% ee, respectively.

In order to obtain more details on this reaction, we then investigated the influence of the nature of the solvent during the hydrogenation of enamide **3** under

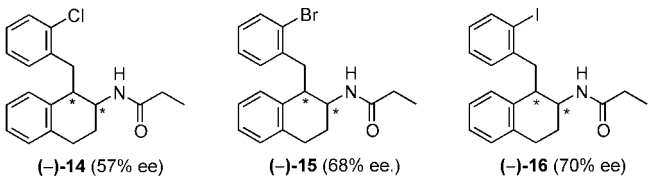


Figure 1.

Table 3. Influence of the nature of the ruthenium precursor on the hydrogenation of the enamide **3**.[a]

Ligand	Acid	Conversion (%)	ee (%)
Me-Duphos	HBF_4	100	68
Me-BPE	HBF_4	100	60
Biphemp	HBF_4	0	0
Binap	HBF_4	0	0
Me-Duphos	HOTf	100	64
Me-BPE	HOTf	100	56
Me-Duphos	HBr	0	0

[a] General conditions: enamide **3** (1 mmol), H_2 (100 bar), 30 °C, 20 h, 0.5 mol % of [Ru*]. [Ru*] cat.: ligand/(COD)-Ru(methallyl)$_2$/acid in the molar ratio: 1/1/2.

100 bar of hydrogen using (Me-Duphos)ruthenium precursors. Methanol seemed to be the solvent of choice. Indeed, whereas propionamide **11** was obtained with 68% ee in methanol, only 30% conversion and 22% ee were reached in toluene.

We also examined both the use of other optically active ligands such as the atropoisomeric Binap and Biphemp, and the nature of the acid used to generate the ruthenium precursors (Table 3).

The use of tetrafluoroboric or triflic acid, in order to generate Me-Duphos and Me-BPE catalysts, led to complete conversion into propionamide **11** with 56 to 68% ee after 20 hours at 30 °C (Table 3). No conversion was observed when HBr was used, which indicated that the coordinating ability of the bromide had a negative effect.[12] It is also noteworthy that the ruthenium species generated from (COD)Ru(methallyl)$_2$, HBF_4, and Binap or Biphemp were inactive. Until now, we have no evidence for the nature of this catalyst, but ^{31}P NMR studies of the solid isolated from the [(*R*,*R*)-Me-Duphos]ruthenium catalytic mixture showed the presence of two ruthenium moieties before addition of hydrogen.

In conclusion, we have reported the first one-pot synthesis of tetrasubstituted enamides by acid-catalyzed direct condensation of primary amides with non-activated cyclic ketones. The use of the easily *in situ*-generated catalytic system based on Me-Duphos or Me-BPE ligands associated to (COD)Ru(methallyl)$_2$ and HBF_4 allowed the hydrogenation of tetrasubstituted enamides with good ee's and a high level of diastereoselectivity. Further studies to improve the catalyst efficiency and to elucidate the reaction mechanism are now under active progress.

Experimental Section

Typical Procedure for Preparation of Ruthenium Precatalysts

Equimolar amounts of (COD)Ru(methallyl)$_2$ and Me-Duphos (or Me-BPE ligand) were dissolved in degassed dichloromethane in a Schlenk tube under inert atmosphere. The solution was then cooled down to 0 °C and 2 equivalents of HBF_4 (54 wt % in Et_2O) were slowly added. After half an hour stirring at 0 °C, the reaction mixture was evaporated to dryness, dissolved in MeOH, and this solution was directly used for hydrogenation of the enamides. The evaporation to dryness allowed the isolation of a crude ruthenium-containing solid, which could also be used for hydrogenation in methanol and led to similar results as the *in situ* prepared methanolic solution.

The ^{31}P NMR of the resulting Me-Duphos complex showed three different phosphorus signals : δ (ppm) = 91.00 (d, *J* = 24.5 Hz), 93.55 (d, *J* = 24.5 Hz), 101.95 (s).

Typical Procedure for Enantioselective Hydrogenation of Enamides 1–8

1 mmol of enamide was added to 0.005 mmol of the ruthenium precatalyst in solution in 8 mL of degassed MeOH in a 125-mL autoclave placed under an inert atmosphere. After degassing with hydrogen, a pressure of 100 bar of hydrogen was applied. The autoclave was mechanically stirred during 20 h at 30 °C and the conversion was determined by ^{1}H NMR of the crude reaction mixture. After isolation of the hydrogenated amides by flash chromatography over silica gel, the enantiomeric excesses were determined by HPLC using a Chiralcel OD 25 column (hexane/isopropanol mixture used as eluent).

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