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Asymmetric hydrogenation of enamides with catalysts containing chiral thiourea ligands

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Abstract

The asymmetric reduction of enamides with molecular hydrogen and catalytic amounts of rhodium, iridium or ruthenium complexes containing chiral N,S-ligands is reported. Various enantiomerically pure mono- and dithioureas were examined. The C_2-symmetry of the dithiourea ligands seems essential to the enantioselectivity achieved. Ee values of up to 70% were observed. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Development of practical asymmetric hydrogenation of olefins was begun 30 years ago by Knowles[1] and Kagan,[2] who focused on the enantioselective reduction of olefinic *N*-acyl-aminoacrylic acids. Since then many catalytic rhodium and ruthenium systems containing chiral diphosphine ligands have been reported to hydrogenate dehydroaminoacids[3] and enamides[4] with more than 90% enantioselectivity. As enantiopure phosphines are often expensive to synthesize and are additionally difficult to recycle, we are interested in replacing them by nitrogen derivatives. Chiral N-ligands are now widely used in asymmetric catalysis[5,6] and the reduction of C=C bonds can be carried out by many different reducing agents, most commonly sodium borohydride or molecular hydrogen. Nitrogen containing ligands such as semicorrins[7] induced high enantioselectivity when sodium borohydride was used, whilst in the case of olefin reduction by molecular hydrogen, most of the chiral nitrogen ligands employed to date have been N,P-ligands or chiral N-ligands linked to non-chiral phosphines.[3,8–11] Some non-phosphorus containing ligands for asymmetric C=C hydrogenations have been developed since Ogho et al. proposed the bis(dimethylglyoximato)cobalt catalysts[12,13] in 1970. Corma et al. studied proline derived ligands and anchored their Rh complexes on modified USY zeolites allowing catalyst

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recovery.[14] Recently, other N-ligands such as symmetric diamines were reported,[15] but there are also S-ligands which are efficient: Claver et al. showed that sugar dithioethers[16] can induce up to 62% enantioselectivity in the asymmetric hydrogenation of acrylic acid derivatives. The promising enantioselectivities observed with various chiral diamines for C=O hydrogenation reactions[17] prompted us to test them in C=C hydrogenations, but no significant asymmetric induction was then observed. We recently developed a new series of chiral N,S-ligands with and without C_2-symmetry: some of those monothiourea and dithiourea ligands have previously afforded good enantioselectivities in the hydroformylation of styrene[18] and in the hydrogen transfer reactions of ketones.[19] Herein we report the use of optically pure mono- and dithioureas in Rh, Ir and Ru catalyzed asymmetric enamide hydrogenation reactions.

2. Results and discussion

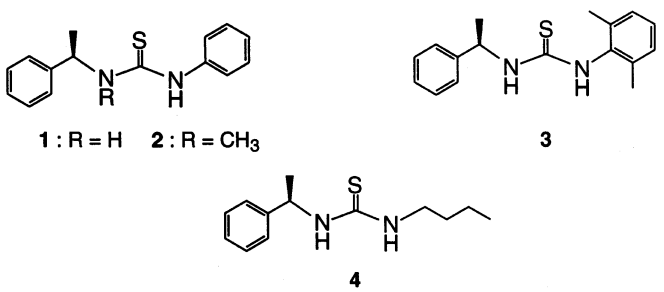
Interactions between thiourea ligands and transition metals in catalytic species are under investigation in our laboratory and theoretical studies are on course.[20] As we have not yet obtained suitable crystals for X-ray studies, the types and number of interactions between the metal center and the functional thiourea group have not been completely established. This encouraged us to study and compare monothiourea ligands with their dithiourea equivalents as chiral catalysts in the hydrogenation of enamides.

2.1. Monothiourea ligands

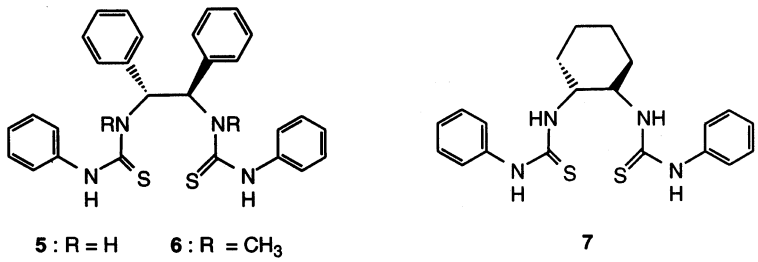
Optically pure monothioureas **1**–**4** (Scheme 1) are easily obtained in more than 70% yield from the corresponding chiral amines and isothiocyanates (see Section 4). The prepared monothioureas were examined in the hydrogenation of both enamides with Rh, Ir or Ru in a 2:1 molar ratio, but despite complete conversion, no significant enantioselectivity was observed (ee <6%). The metallic particles formed during the reactions suggest that monothioureas do not coordinate even if used in large excess (5 equivalents per metal atom).

2.2. Dithiourea ligands

Ligands **5**–**7** (Scheme 2) were obtained from the corresponding optically pure diamines in the presence of two equivalents of phenylisothiocyanate. These dithiourea compounds are very stable and therefore easy to handle and store but most of all, they appear to be more promising than their diamine precursors as chiral inducers for the enamide hydrogenations studied here.



Scheme 1. Chiral monothioureas used in hydrogenation reactions

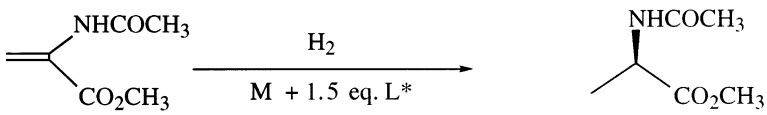


5 : R = H **6** : R = CH_3 **7**

Scheme 2. Chiral dithioureas used in hydrogenation reactions

The reduction of methyl-2-acetamido acrylate and α-acetamidocinnamic methyl ester was carried out under hydrogen catalyzed by Rh, Ir or Ru complexes of thioureas **5**–**7**. The N,S-ligands were combined in various ligand to metal molar ratios in MeOH solutions of the metallic precursors (unless otherwise stated) before their use in the hydrogenation reactions. The results obtained with iridium are not reported here since the observed enantioselectivity was poor (ee <15%) when iridium was combined with any of the chiral ligands studied. In order to compare ligand effects, we gathered the results in two tables depending on the nature of the substrate. The first results with DIOP are also listed to allow comparisons. Table 1 concerns the hydrogenation of methyl-2-acetamido acrylate and Table 2 shows the results obtained from studies on the hydrogenation of α-acetamidocinnamic methyl ester hydrogenation.

Table 1
Dithioureas as chiral catalytic ligands for the hydrogenation of methyl-2-acetamido acrylate

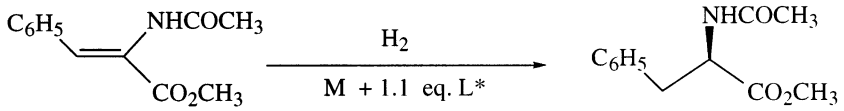


[enamide] = 0.5 M in MeOH; 50 bars; 50°C; 15 hrs, 5% [Metal/L*]

Entry	L*	Metal	% Yield	% Ee (*R*)
0	**DIOP**[a]	$[RhCl(COD)_2]_2$	96[a]	73[a]
1	**5**	$[Rh(COD)_2]BF_4$	65	17
2	**5**	$Ru(COD)(\eta^3\text{-}C_4H_7)_2$	71	26
3	**6**	$[Rh(COD)_2]BF_4$	100[b]	2[b]
4	**6**	$Ru(COD)(\eta^3\text{-}C_4H_7)_2$	96[b]	3[b]
5	**7**	$[Rh(COD)_2]BF_4$	67	30
6	**7**	$Ru(COD)(\eta^3\text{-}C_4H_7)_2$	70	38
7	**7**	$Ru(COD)(\eta^3\text{-}C_4H_7)_2$	75[c]	48[c]
8	**7**	Ru(COD)(COT)	92[c]	61[c]

[a] From Ref. 2: Sub/Rh = 150; 1.1 atm H_2, ex situ prepared Rh/DIOP complex.
[b] Grey particles formed in the reaction mixture.
[c] In THF instead of MeOH.

Table 2
Dithioureas as chiral catalytic ligands for the hydrogenation of α-acetamidocinnamic methyl ester



[enamide] = 0.5 M in MeOH; 40 bars; 50°C; 15 hrs, 1% [Metal/L*]

Entry	L*	Metal	% Yield	% Ee (*R*)
0	**DIOP**[a]	$[RhCl(COD)_2]_2$	90[a]	55[a]
1	**5**	$[Rh(COD)_2]BF_4$	90	19
2	**5**	$Ru(COD)(\eta^3\text{-}C_4H_7)_2$	84	37
3	**6**	$[Rh(COD)_2]BF_4$	30[b]	4[b]
4	**6**	$Ru(COD)(\eta^3\text{-}C_4H_7)_2$	28[b]	5[b]
5	**7**	$[Rh(COD)_2]BF_4$	86	39
6	**7**	$Ru(COD)(\eta^3\text{-}C_4H_7)_2$	96	42
7	**7**	$Ru(COD)(\eta^3\text{-}C_4H_7)_2$	99[c]	58[c]
8	**7**	Ru(COD)(COT)	100[c]	70[c]

[a] From Ref. 2: Sub/Rh = 150; 1.1 atm H_2, ex situ prepared Rh/DIOP complex.
[b] Grey particles formed in the reaction mixture. Conversions are complete, the by-product being $C_6H_{10}CH_2C(CO_2CH_3)COCH_3$.
[c] In THF instead of MeOH.

For Rh as well as for Ru, the presence of a Me group (ligand **6**) instead of a H atom (ligand **5**) on the nitrogen atoms of the central chiral core leads to poor enantioselectivity, and metallic particles were observed in the reaction mixtures.[21] This may be due to the fact that **6** is not coordinated strongly enough to Rh or Ru and the metallic particles formed led to high racemic hydrogenation rates. In fact, Cauzzi et al. showed that even if the thiourea group is mainly coordinated through the sulfur atom to a Rh center, a H atom on the neighbouring nitrogen helps to stabilize the active hydridic species and, in one of the rare X-ray structures of a thiourea rhodium complex, [Rh(COD)(Hbztu)Cl], an intramolecular hydrogen bond was determined.[22]

We have observed that for both metals, Rh and Ru, the presence of the central cyclohexyl group allows better asymmetric induction than the diethylene diphenyl central group, while activity remains the same (entries 5 versus 1).

For ligands **5** and **7**, ruthenium species are more enantioselective than rhodium catalysts (entries 1 versus 2 and 5 versus 6). As the neutral ruthenium precursors employed have little solubility in MeOH, we used various common solvents (CH_2Cl_2, toluene, pentane), the most suitable was found to be dried THF, which may stabilize the intermediate complexes by coordinating to the ruthenium center. It is notable that the replacement of the methylallyl groups (entry 7) by a cyclooctatriene (COT) ligand (entry 8) in the ruthenium precursor improves both activity and enantioselectivity. The active species thus seems easily formed after one COT hydrogenation rather than two $\eta^3\text{-}C_4H_7$ hydrogenations. The 61% ee value obtained for methyl-2-acetamido acrylate hydrogenation is moderate but it prompted us to test an activated substrate such as α-acetamidocinnamic methyl ester (see Table 2).

The same trends are seen for α-acetamidocinnamic methyl ester as those in the hydrogenation of methyl-2-acetamido acrylate. A hydrogen atom is needed on the central nitrogen atoms to

allow effective ligand coordination (entries 1 and 2 versus 3 and 4), the presence of a chiral cyclohexyl core enhances enantioselectivity (entries 1 and 5 and 2 and 6) and Ru species are more active and enantioselective than Rh complexes (entry 5 versus entry 6). The presence of the phenyl group on the enamide substrate increased both activity and enantioselectivity. This has already been observed with Rh/DIOP and various asymmetric hydrogenation catalysts.[2–5] Dithiourea **7** thus led to 70% ee in the hydrogenation of α-acetamidocinnamic methyl ester. Even if this enantioselection is far from the >99% ee obtained with MeDUPHOS[23] or BINAP[24] chiral diphosphines, it is one of the first examples of significant asymmetric enamide hydrogenation by non-phosphorus ligands. The N,S-ligands we have developed also offer a potentially good alternative to phosphorus ligands since they are easier to obtain, and handle, than chiral diphosphines.

A common point observed in P- and N,S-ligands used in asymmetric enamide hydrogenation is the general need for C_2-symmetry of the chiral inducers. This symmetry reduces the number of complexes which can be formed by coordination of the ligand to the metal center. The formation of C_2-symmetric complexes is then favoured when chelating dithiourea ligands are used instead of monothioureas, enhancing the enantioselection of the active species. Finally, we can point out that the more strained dithiourea **7** is a better asymmetric inducer than its analog **5**. The rigidity of the ligand backbone has been recently reported[25] to be related to enantioselection improvements for bis(phospholano)ethane ligands.

3. Conclusion

Asymmetric enamide hydrogenation was carried out with N,S-ligands and rhodium or ruthenium catalysts giving enantioselectivities up to 70%. Two types of enantiomerically pure ligands, monothioureas and dithioureas have been tested, but only dithioureas provided significant enantioselection. This suggests that for enamide hydrogenation the C_2-symmetry of the dithiourea ligands is a key factor in the degree of control observed. Even if more active and enantioselective catalysts are formed with bidentate P-ligands, the easy to obtain and stable dithioureas **5** and **7** are interesting alternatives for asymmetric enamide hydrogenation. This is important since enantiomerically pure ligand availability is directly related to the price of a chiral catalyst. The robustness of these new chiral inducers may facilitate the identification of the active species and aid catalyst recovery. Thus, we focus on the ex situ preparation and characterization of the ruthenium–dithiourea **7** species. We are also interested in the polymerization of the dithiourea ligands in order to obtain reusable catalysts.

4. Experimental

4.1. General

Solvents were degassed before use by prolonged argon bubbling for MeOH, cyclooctadiene and pentane or by distillation under a nitrogen atmosphere for THF. Ethyl-2-acetamido acrylate, α-acetamidocinnamic methyl ester from Aldrich® and $RuCl_3 \cdot 7H_2O$, $[Rh(COD)Cl]_2$ and $Ru(COD)(\eta^3\text{-}C_4H_7)_2$ from Strem Chemicals were used. Gas chromatography analyses were carried out with a JW DB-1701 (non-chiral) or a Lipodex A (chiral) 25 m column on Shimadzu GC-14A chromatographs using flame-ionization detector and Shimadzu C-R6A integrators.

4.2. Catalytic precursors

$[Rh(COD)_2]BF_4$ was prepared from $[Rh(COD)Cl]_2$ and $AgBF_4$ as already described.[26] $Ru(COD)(\eta^3\text{-}C_4H_7)_2$ was used as received and Ru(COD)(COT) was prepared according to the published procedure.[27]

4.3. Monothioureas **1–4**

The enantiomerically pure amine was added to a stoichiometric amount of desired isothiocyanate in CH_2Cl_2 and the solution was stirred overnight at room temperature. The reaction mixture was then poured into a large excess of cold pentane to allow monothiourea precipitation. The product was filtered and washed before drying under vacuum. Spectroscopic data were compared to those already published.[18]

4.4. Dihioureas **5–7**

Dithioureas were prepared following the same experimental procedure as that for monothiouras, except that two isothiocyanate equivalents are needed per amine molecule. Enantiomerically pure diamines used were (1*R*,2*R*) cyclohexanediamine from Aldrich® and (1*R*,2*R*)-(+)-*N*,*N*′-dimethyl-1,2-diphenyl-1,2-ethylenediamine prepared according to recently published procedures.[28] Spectroscopic data of obtained dithioureas **5–7** were compared to those we have already published.[17,19,29]

4.5. Enamide hydrogenations

A typical enamide hydrogenation test was carried out as follows: the metallic precursor was added under an argon atmosphere to a degassed and dried MeOH (or THF) solution of the chiral ligand. After stirring for 30 minutes, the substrate was added and the resulting solution was transferred to a purged stainless steel autoclave and pressurized with H_2. After stirring overnight at 50°C the autoclave was cooled and degassed. The reaction mixtures were then filtered through Celite and analyzed by chiral gas chromatography (60 m βdex 225 column) for the hydrogenation of methyl-2-acetamido acrylate or by gas chromatography (25 m JW-DB-1701 column) and chiral HPLC (25 m Chiralcel OD column) for the hydrogenation of α-acetamidocinnamic methyl ester.

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