Dithiourea Ligands in the Rhodium-Catalyzed Hydride-Transfer Reduction of Ketones − A Theoretical and Experimental Approach

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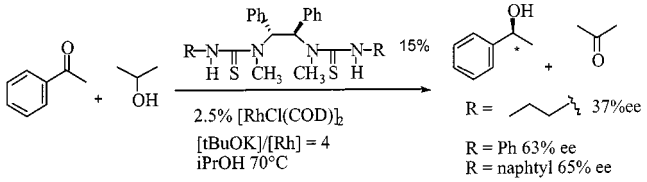
Keywords: Asymmetric catalysis / Rhodium / Thioureas / Ketone reduction / Theoretical calculations

Various dithioureas bearing an aromatic ring on their terminal nitrogen atoms have been synthesized. These have been tested in the asymmetric reduction of ketones as catalyzed by a rhodium complex. The influence of electron-withdrawing and electron-donating substituents on the aromatic rings on the reactivity and the enantiomeric excess (*ee*) has been assessed. The coordination modes of a model thiourea have been studied by Density Functional Theory (DFT) calculations. The electronic effects have also been analyzed and an interpretation of the variation in the enantiomeric excess, based on a supposed change in the coordination mode, is given.

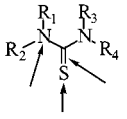
Introduction

The successful use of thioureas as ligands for the asymmetric metal-catalyzed hydride-transfer reduction of ketones has recently been described.[1,2] To the best of our knowledge, this family of ligands has seldom been used in asymmetric catalysis and only little is known about the way in which these ligands are coordinated to the metal center. Thus, Brunner et al.[3] have reported the synthesis of a chiral rhodium complex with thioamide ligands as well as its characterization by means of an X-ray structure analysis. Its analysis revealed a binuclear Rh complex, where the two metal atoms are bound by the sulfur atoms of the two thioamide ligands. The other coordination sites are occupied by the cyclooctadiene (COD) ligand. Cauzzi et al.[4] have described the structure of the complex [(COD)(*N*,*N*′-diphenylthiourea)RhCl]. The X-ray structure analysis showed that the thiourea ligand is also bound to the Rh center through the sulfur atom. In the course of our studies on the use of nitrogen ligands in asymmetric catalysis, we have determined the structure of the catalytic complex in the rhodium-catalyzed asymmetric hydride-transfer reduction of ketones with diamine ligands using a dual experimental and theoretical approach.[5,6] We have now synthesized dithioureas and have followed the same strategy to elucidate the way in which they are coordinated to the rhodium center. We have previously shown[2] that the nature of the substituents on the nitrogen atom of the dithiourea ligand has a considerable influence on the reaction and that aromatic substituents are better than aliphatic ones (Scheme 1).



Scheme 1. Enantioselective hydride-transfer reduction of acetophenone using dithiourea ligands

In order to design a more efficient and selective "tailor-made" catalyst, it is of great importance to know the type of interaction involved between the metal center and the thiourea ligands (Scheme 2).



Scheme 2. Various possible binding sites of the thiourea ligands

Both the sulfur and nitrogen atoms could be coordinated to the metal center, as well as a C=S double bond or one of the C=N double bonds of the mesomeric form. The thiourea functional group could be a two- or four-electron-donating ligand. Moreover, when a hydrogen atom is attached to one of the nitrogen atoms, it can be abstracted, depending on the experimental conditions, which leads to a type X ligand (one-electron donor). Hydrogen bonds may also be involved, as is the case with a chlorine atom in ref.[4a]

In this work, the effects of structural modifications of both the ligand and the substrate on the enantiomeric excess (*ee*) and conversion have been studied. For this purpose, we have synthesized and tested various aromatic thioureas bearing either bulky groups, electron-withdrawing or -donating groups. Various ketones with electron-withdrawing or -donating substituents in the *para* position have

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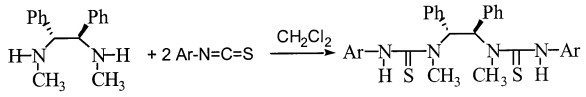
also been used as substrates. This study has been complemented by theoretical calculations.

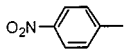
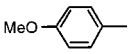
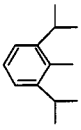
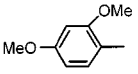
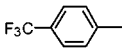
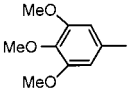
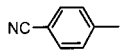
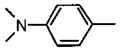
Dithiourea Synthesis

The dithioureas were synthesized by the addition of two isothiocyanate moieties to one (*R*,*R*)-*N*,*N*′-dimethyl-1,2-diphenylethylenediamine unit at room temperature in CH_2Cl_2. The products were isolated by filtration after precipitation in pentane (Scheme 3 and Table 1).



Scheme 3. Dithiourea synthesis

Table 1. Various dithioureas synthesized according to Scheme 3

Entry	Dithiourea (Ar =)	Isolated yield (%)	Entry	Dithiourea (Ar =)	Isolated yield (%)
1	 **1**	70	6	 **6**	11
2	 **2**	71	7	 **7**	87
3	 **3**	0	8	 **8**	80
4	 **4**	43	9	 **9**	78
5	 **5**	96	10	 **10**	79

The introduction of bulky substituents on the aromatic ring can be expected to influence the coordination pattern of the ligand and thereby modify the reactivity of the complex. Therefore, we synthesized thiourea **2**, which was isolated in its pure form without further purification in good yield (71%). All attempts to obtain compound **3** led to a mixture of several products that was difficult to separate. Steric factors might explain these observations.

Electronic factors may also play an important role in the asymmetric induction. In the case of electron-withdrawing groups, products **4** and **5** were obtained in good to excellent isolated yields, but the synthesis of thiourea **6** led to a mixture of mono- and dithioureas along with degradation products. Compound **6** was found to be light-sensitive and particular care was needed to prevent its decomposition. After chromatography on SiO_2, the pure thiourea **6** was obtained in low yield and was kept under an inert gas.

Compounds with electron-donating groups, which increase the electron density of the ligands, were also synthesized. This family of compounds was obtained in very good isolated yields (78−87%).

Acetophenone Reduction

Effects of Phenyl Substitution

The various ligands shown in Table 1 were tested in the reduction of acetophenone under identical reaction conditions. These reaction conditions were essentially chosen for their high reproducibility with regard to both conversion and selectivity, even though they are not the optimal ones in terms of selectivity.

The results obtained with ligands bearing bulky substituents in the vicinity of the nitrogen atoms are reported in Table 2. In both cases, (*S*)-phenylethanol was preferentially obtained and the activity and selectivity were quite similar. The enantiomeric excess is the most salient characteristic for synthetic applications. Nevertheless, the (*R*) and (*S*) isomers are formed through two competing reactions and therefore the (*S*)/(*R*) ratio corresponds to the ratio of the rate constants and should be more representative of the ligand effect. In the present case, the (*S*)/(*R*) values were almost the same. These results indicate that steric hindrance around the nitrogen atoms bound to the aromatic rings has only a slight influence on the reaction course. Thus, we assume that the dithiourea is unlikely to complex the rhodium ion through these nitrogen atoms.

Table 2. Reduction of acetophenone using dithioureas with bulky substituents; conditions: see Exp. Sect.

Entry	Ligand	Conversion [%]	*ee* [%] (configuration)	(*S*)/(*R*)
1	**1**	97	63 (*S*)	4.4
2	**2**	92	66 (*S*)	4.9

The results obtained with dithioureas bearing electron-withdrawing and -donating groups are reported in Table 3 and 4, respectively. The Hammett (σ) coefficients are also given since the electronic effects of the substituents on the aromatic ring can be classified according to these values. Both the catalytic activity and the selectivity can be seen to decrease with the introduction of an electron-withdrawing group if we compare dithioureas **4**, **5**, and **6** with dithiourea **1**. The *ee* values obtained were very low (around 15%) and thus the (*S*)/(*R*) ratio decreased from 4.4 to 1.2. The activity also decreased. Nevertheless, introduction of a CN group (Table 3, Entry 3) with $\sigma = 0.70$ led to a higher conversion than introduction of a CF_3 group (Table 3, Entry 2) with a σ of only 0.54. Hence, the activity does not follow the order given by σ. Several hypotheses may be proposed to explain the overall loss of activity and selectivity. Electron-withdrawing groups decrease the electron density on the atoms

Table 3. Reduction of acetophenone using dithioureas with electron-withdrawing substituents; for conditions see Exp. Sect.

Entry	Ligand	Hammett coefficient σ≅[a]	Conversion [%]	*ee* [%] (configuration)	(*S*)/(*R*)
1	**1**	0	97	63 (*S*)	4.4
2	**4**	0.54	60	15 (*S*)	1.4
3	**5**	0.70	85	12 (*S*)	1.2
4	**6**	0.78	42	14 (*S*)	1.3

[a] From: J. March, *Advanced Organic Chemistry*, 4th ed., John Wiley and Sons, New York, **1992**, p. 244.

Table 4. Reduction of acetophenone using dithioureas with electron-donating substituents; for conditions see Exp. Sect.

Entry	Ligand	Hammett coefficient σ≅[a]	Conversion [%]	*ee* [%] (configuration)	(*S*)/(*R*)
1	**1**	0	97	63 (*S*)	4.4
2	**9**	−0.08[b]	93	70 (*S*)	5.7
3	**7**	−0.28	96	71 (*S*)	5.8
4	**8**	−	97	75 (*S*)	6.9
5	**10**	−0.63	99	65 (*S*)	4.7

[a] From J. March, *Advanced Organic Chemistry*, 4th ed., John Wiley and Sons, New York, **1992**, p. 244. − [b] $\sigma_p + 2 \times \sigma_o = -0.28 + 2 \times 0.10$.

bound to the Rh center and thus they may also decrease the stability of the metal complex. The ligand could then be replaced by other nonchiral ligands such as *i*PrOH. Moreover, the hydride ion becomes less electronegative, which decreases its interaction with the ketone (electrophile).

With electron-donating groups, the reverse effect was observed. The activity remained almost constant compared to that of ligand **1** and the (*S*)/(*R*) ratio increased from 4 to up to 7 (Table 4, Entry 4). Nevertheless, with the dithiourea **10**, which has a higher σ coefficient, virtually no effect was noticed compared to **1**. It is possible that the NMe_2 group attached to the aromatic ring competes with the other N atoms or with the S atoms of the ligand in complexing the metal center, which thus modifies the selectivity.

Effects of Ketone Substitution

In view of the marked influence of the presence of electron-withdrawing or -donating groups on the aromatic ring of the ligand, we also studied the influence of such groups on the aromatic ketone substrates. Thus, *para*-trifluoromethyl- and -methoxyacetophenone were reduced under standard conditions with various dithiourea ligands.

An electron-withdrawing group attached to the aromatic ring of the substrate increases the positive charge on the carbon atom of the carbonyl group and thus facilitates the hydride transfer. With ligand **1**, the experimental data are consistent with this hypothesis since almost complete conversion was achieved within 50 h (Table 5, Entry 1) as opposed to after 70 h in the case of unsubstituted acetophenone (Table 2, Entry 1). With ligands bearing either electron-withdrawing or -donating groups, however, the activity decreased. Steric factors and hydrogen bonding with the solvent may be invoked to account for this behavior.

Table 5. Reduction of *para*-trifluoromethylacetophenone with various ligands; reaction time 50 h; for further conditions see Exp. Sect.

Entry	Ligand	Conversion [%]	*ee* [%] (configuration)	(*S*)/(*R*)
1	**1**	99	29 (*S*)	1.8
2	**4**	28	8 (*S*)	1.2
3	**8**	35	34 (*S*)	2.0

Irrespective of the ligand, the reduction of *para*-trifluoroacetophenone occurred with lower selectivities. Nevertheless, the best selectivity was obtained with electron-donating groups attached to the ligand (34% *ee*, Table 5, Entry 3) as opposed to 29% *ee*. These results could be interpreted in terms of the formation of a donor−acceptor complex between the substrate and the ligand. To test this hypothesis, *para*-methoxyacetophenone was reduced (Table 6). The activity decreased considerably with this substrate, which can be explained in terms of the less favorable hydride attack on the less electrophilic carbonyl group. The difference in selectivity was nevertheless significant as it was measured at low conversion. An electron-donating group attached to the ligand led to a better selectivity, while an electron-withdrawing one led to a lower selectivity. This result is inconsistent with the formation of an intermediate donor−acceptor complex. On the contrary, the electron density on the thiourea appears to be a key factor in determining both the selectivity and efficiency.

In conclusion, the experimental approach to analyzing the enantioselective hydride-transfer catalyzed by (thiourea)rhodium complexes gives rise to several hypotheses

Tble 6. Reduction of *para*-methoxyacetophenone with various dithioureas; reaction time 17 h

Entry	Ligand	Conversion [%]	*ee* [%][a]	Ratio[b]
1	**1**	6	54	3.3
2	**4**	3	43	2.2
3	**8**	4	68	4.3

[a] Absolute configuration undetermined, *ee* measured by HPLC; for other conditions see Exp. Sect. – [b] Ratio of the two isomers.

concerning the structure/properties relationship. Firstly, the presence of bulky substituents in the vicinity of the nitrogen atom bound to the aromatic part of the thiourea has been shown to have little or no effect on either the selectivity or the reaction rate. Therefore, this nitrogen atom is unlikely to be a binding site in the metal complex. Secondly, electron-withdrawing groups attached to the aromatic substituents have been shown to have a dramatic negative effect on both the selectivity and efficiency of the catalytic system. On the contrary, an electron-donating group has been found to have a marked positive effect on the enantioselectivity of the hydride transfer. These results are broadly consistent with the Hammett coefficients, since substituents with a positive σ value give a lower selectivity, while those with a negative σ value give a higher selectivity. Nevertheless, within each group of σ coefficients (positive or negative), no relationship exists between the relative order and the *ee* values (compare Entries 3 and 5 in Table 4). Studies on the effects of substituents on the aromatic part of the substrate clearly show that these results cannot be attributed to donor−acceptor interactions between the substrate and the ligand. Instead, they are probably due to modification of the electron density around the binding site of the ligand. Clearly, thioureas represent potential new ligands for asymmetric catalysis, but more information concerning the coordination sites will be necessary in order to design better ligands. Unfortunately, such information cannot be obtained by direct observation because of the lack of X-ray structures of the catalytic species. Consequently, we undertook a theoretical study in the hope of gaining insight into the problems that arose in the experimental study.

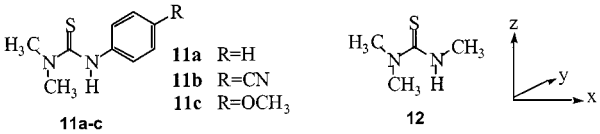
Theoretical Study

We first compared the possible coordination modes of the thiourea functional group towards the rhodium center. Thereafter, we studied the electronic effects of substituents on the aromatic ring in relation to the previous experimental results.

Computational Details

The calculations were based on Density Functional Theory (DFT) at the generalized gradient approximation (GGA) level. They were performed with the Gaussian 94 program.[8] We used Becke's 1988 gradient-corrected functional[9] for exchange and Perdew−Wang's 1991 gradient-corrected functional[10] for correlation. For the Rh atom, we used the relativistic effective core potential of Hay and Wadt with the corresponding double ζ basis set.[11] A pseudopotential was also used for the core electrons of the C, N, and O atoms.[12] The corresponding valence basis set was of the 4-1G type[13] with a d polarization function on N (α = 0.80), C (α = 0.75), and O (α = 0.85). For H atoms, we used the Duning double ζ basis set and added a p polarization function on the hydride (α = 1.00).

All the structures were fully optimized using the gradient technique. The dithioureas used experimentally were too large to be considered in the theoretical study. Therefore, we performed the calculations on the monothiourea **11**, in which the second moiety of the dithiourea is replaced by a methyl group (Scheme 4). **11** was successively substituted with the electron-withdrawing CN group and the electron-donating OCH_3 group.

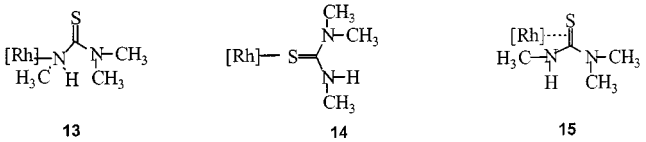


Scheme 4. The thioureas under study

In a previous study, we showed that the supposed hydride complex intermediate of the carbonyl reduction retains one COD ligand, which we modelled with two ethylene molecules.[5] Thus, we studied the coordination modes of a thiourea towards the 16e$^-$ fragment $RhH(NH_3)(C_2H_4)_2$, where the coordination sphere is completed by an NH_3 ligand. To save computational time, we still simplified the thiourea and replaced the phenyl ring by a methyl group. Thus, $NHCH_3-CS-N(CH_3)_2$ (**12**) (Scheme 4) was used as a model to study the coordination modes.

Thiourea Coordination Modes

Three possibilities exist for the coordination of a thiourea ligand to a metal ion, i.e. through one nitrogen atom (**13**), through the sulfur atom (**14**), or through the π_{CS} system (**15**). These are shown in Scheme 5 in the case of thiourea **12**. For **13** or **14**, the main interaction is the donation of the lone pair of N or S into a vacant orbital of the metal ion. In the case of **15**, the main interaction is a back-donation from the metal ion to the π^*_{CS} orbital, the π_{CS} orbital being too low in energy to significantly interact with the metal ion. The C=S bond gives rise to the same types of coordination structures as the C=O bond of aldehydes or ketones (η_1 and η_2). Nevertheless, with S being less electronegative than O, the main orbitals, π, π*, and the lone pairs are higher in energy and hence the relative stability order of the η_1 and η_2 forms can be different for thioureas.



[Rh] = $RhH(NH_3)(C_2H_4)_2$

Scheme 5. Various coordination modes of thiourea **12** towards rhodium

The geometry optimization of **13** did not give a stable structure: The thiourea ligand did not remain bound to the metal center and the square-planar $16e^-$ ML_4 complex $RhH(NH_3)(C_2H_4)_2$ was obtained. This complex has been described previously.[14] The geometry optimizations of **14** and **15** gave the structures shown in Figure 1. Both are trigonal-bipyramidal complexes with an axial hydride, like those studied previously.[5] In **14**, the thiourea ligand is bound to Rh through the lone pair of the sulfur atom. The Rh−S bond (2.53 Å) is longer than that quoted in ref.[4] (2.40 Å). This may be due to the higher Rh coordination in **14** (ML_5 complex vs. ML_4 for the experimental complex), which leads to a weaker bond. The C=S double bond is slightly elongated compared to that in the free thiourea (1.73 vs. 1.69 Å), in agreement with the X-ray data. The C=S bond lies almost in the basal plane (C_1SRhH dihedral angle = 66°). A small interaction with the π-CS system can thus occur, which lengthens the C−S bond. The thiourea moiety remains planar (N_1C_1SH = 5° and N_2C_1SH = −176°). Another structure, starting with the C=S bond parallel to RhH, was also optimized. The C=S bond formed an angle of 30° with the RhH bond and the RhS bond became longer (2.60 Å). This second structure was less stable than **14** by 5.8 kcal/mol.

In **15**, the thiourea ligand is bound to Rh through both its S and C atoms, in an η_2 coordination mode similar to that seen for olefins. As in **14**, the Rh−S and Rh−C^1 bonds are rather long (2.5 Å). The C−S bond is more elongated than that in **14** (1.76 Å) because of the back-donation into the vacant π^*_{CS} orbital. The amine substituents $NH(CH_3)$ and $N(CH_3)_2$ are bent away from the rhodium center (N_1 by 8.3° and N_2 by 10.1°). As regards the relative stabilities, **14** is more stable than **15** by 9.0 kcal/mol, which indicates that thiourea **12** prefers the η_1 coordination mode over the η_2 mode, in agreement with the complex found experimentally.[4] The adoption of this coordination mode can be rationalized by considering at the orbitals of thiourea **12**, the geometry of which was also optimized. The main components and energies of these orbitals are shown in Table 7. The HOMO of **12** is a sulfur lone pair; thus, with the π_{CS} orbital being much lower in energy and the LUMO (π^*_{CS}) being rather high, the best coordination involves this lone pair, thereby giving **14**. This is in contrast to ketones, which prefer η_2 coordination. As mentioned above, the interacting orbitals are higher in energy for C=S than for C=O. This favors the interaction of the lone pairs on S with the metal ion, giving the η_1 form, and simultaneously decreases the

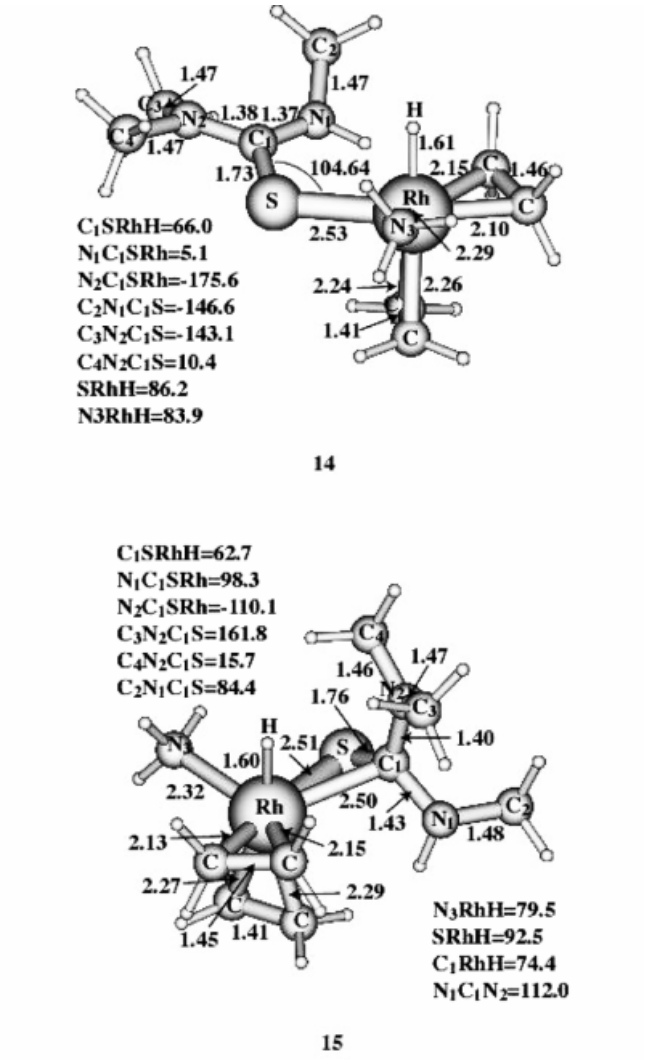


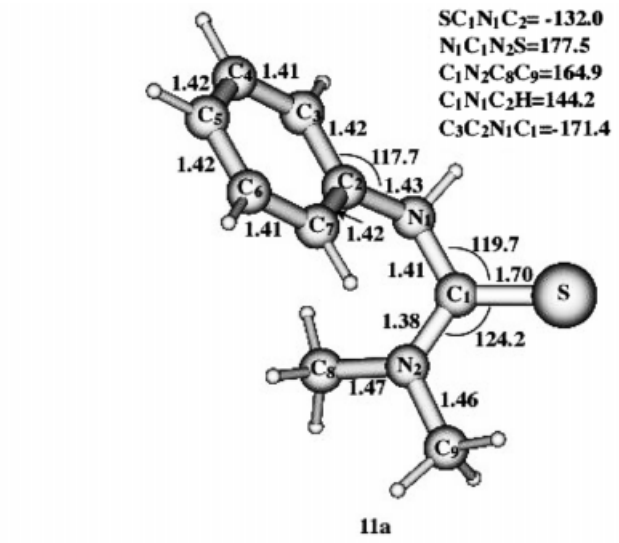
Figure 1. Optimized geometries of rhodium complexes **14** and **15**; lengths in Å, angles in °

Table 7. Most important orbitals of thioureas **11a**−**c** and **12**; main components and energies in eV; differences compared with the orbitals of **11a** are given in parentheses

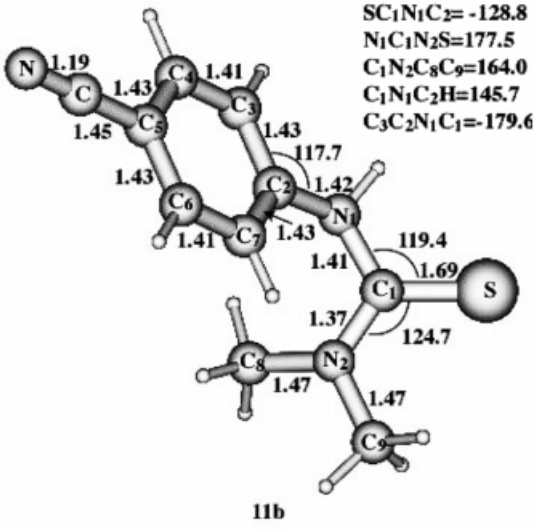
Orbital	Main components	Energy			
		11a	**11b**	**11c**	**12**
1	π^*_{CS}, pN_1, pN_2, π*Φ	−0.65	−1.48 (−0.83)	−0.46 (+0.19)	
2	π*Φ	−1.27	−1.89	−1.22	
3 LUMO	π^*_{CS}, pN_2, π*Φ	−1.54	−2.42 (−0.88)	−1.36 (+0.18)	−1.06
4 HOMO	p_1S, ε pN_1	−4.52	−4.97 (−0.45)	−4.39 (+0.13)	−4.36
5	p_2S, pN_1, pN_2, π_{CS}	−5.12	−5.61 (−0.49)	−4.93 (+0.19)	−5.01
6	pN_1, pN_2	−5.41	−5.88 (−0.47)	−5.07 (+0.34)	−5.73
7	πΦ	−6.25	−6.93	−6.22	
8	π_{CS}, pN_1, pN_2	−6.89	−7.27	−6.33	−7.99

back-donation into π^*_{CS}, which reduces the propensity for η_2 coordination.

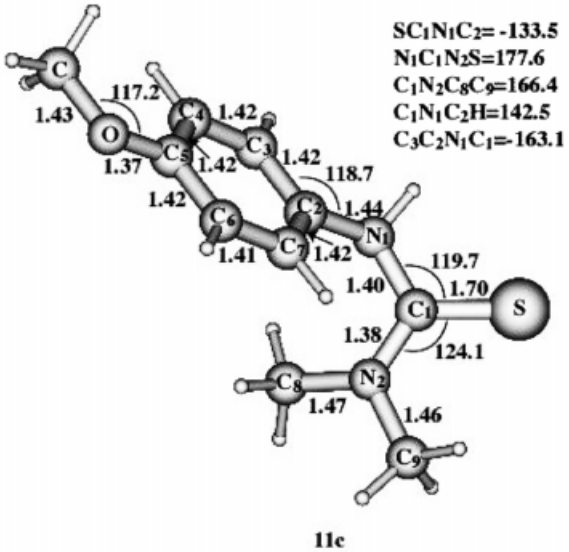
The nitrogen lone pairs appear mainly in orbital 6, which is relatively low in energy. Consequently, the interaction of the nitrogen atoms with the metal ion is not sufficiently strong to ensure the coordination of the thiourea ligand. For comparison, the HOMO of the *N*,*N*′-dimethyl-1,2-dimethylethylenediamine ligand $[NH(CH_3)CH(CH_3)]_2$, which coordinates to Rh,[15] lies at −4.42 eV and corresponds to an out-of-phase combination of the nitrogen lone pairs. The effect of the electron-withdrawing C=S double bond in **12** is to lower the energy of the lone pairs on N, thereby preventing the coordination of the thiourea ligand through its N atoms.



11a



11b



11c

Figure 2. Optimized geometries of thioureas **11a**−**c**; lengths in Å, angles in °

Substituent Effects on 11

In the preceding section, we have shown that the thiourea coordination mode depends on the shape and the relative position of the interacting orbitals. We will now focus on how the orbitals of thiourea **11** are modified when substituents are attached to the phenyl ring. The optimized structures obtained for **11a**−**c** are given in Figure 2. The geometry does not vary greatly when the substituent is changed. Some points can be noted: The C−S bond length (ca. 1.70 Å) is in agreement with the experimental X-ray results obtained for a phenyldithiourea.[4] The phenyl−N_1−C_1 moiety is almost planar, with the dihedral angle C_3−C_2−N−C_1 measuring −171.4, −179.6, and −163.1° in **11a**, **11b**, and **11c**, respectively. The four atoms C_1, S, N_1, N_2 are also coplanar (dihedral angle of 177.5° in **11a** and **11b** and of 177.6° in **11c**) and these two planes form an angle of 47−51° (the dihedral angle S−C_1−N_1−C_2 varies from −133.5 to −128.8°); this is in agreement with the value found experimentally.[4] Atom N_2 is less pyramidal than N_1, with a C_1−N_2−C_7−C_8 dihedral angle of 164−166° as opposed to a C_1−N_1−C_2−H dihedral angle of 142−146°. The lone pair on each nitrogen atom is almost parallel to the π_{CS} system and that on N_1 is also almost parallel to the π_{phenyl} system. The CN and OCH_3 substituents lie in the phenyl plane [the dihedral angle H_3C−O−C−C is 179.4°]. This allows conjugation of the π_{CN} system and the oxygen lone pair with the phenyl π system. As a result, the thioureas **11a**−**c** are almost fully conjugated and the orbitals are delocalized over the whole molecule. Nevertheless, in each orbital one component prevails over the others.

The shapes and energies of the orbitals vary when the substituents are changed. This is shown in Table 7, where the most important occupied and unoccupied orbitals are considered. In the same table, the orbitals of thiourea **12** are also given. For each orbital, the main component is in italics. The orbitals of the four thioureas are of the same shape. Compared to the orbitals of **12**, those of **11a** are lowered in energy by the presence of the phenyl ring. Never-

theless, π^*_{CS} is still high and thus the coordination is most likely to take place through the S atom as seen for **12**.

Compared to the orbitals of **11a**, those of **11b** are all stabilized by the influence of the electron-withdrawing CN group. The most stabilized is the π^*_{CS} orbital, which, besides this effect, is further stabilized by an in-phase mixing with one phenyl π^* orbital containing a contribution from π^*_{CN}. Thus, the interaction of the lone pair on S will be weaker and, conversely, the back-donation into π^*_{CS} will become more important. Therefore, taking into account the small energy difference between the model complexes **14** and **15**, the coordination of **11b** to Rh can change from η_1 to η_2. This may explain the dramatic decrease in *ee* observed when the phenyl ring bears electron-withdrawing substituents.

On the contrary, all the orbitals of **11c** are destabilized by the electron-donating OCH_3 group. Orbital 6 is even more destabilized by an out-of-phase mixing with a phenyl π orbital containing a contribution from an oxygen lone pair. However, the destabilizing effect of OCH_3 is smaller than the stabilizing effect of CN, and the overall effect is that the orbitals of **11c** are not very different from those of **11a**. Hence, the coordination mode must be the same, which accounts for the fact that the reactivity of **11c** is not very different from that of **11a**.

Thus, the electron-withdrawing CN group has a larger effect than the electron-donating OCH_3 group. This is partly due to the fact that the conjugation of the entire molecule is greater for CN than it is for OCH_3, as evidenced by the values of the relevant $C_3-C_2-N_1-C_1$ dihedral angles (−179.6 and −163.1°, respectively), which allows for better electronic communication.

Conclusion

Both the experimental and theoretical studies described in this article indicate that the coordination of the dithioureas takes place through the S atom. As a consequence, thiourea should be considered as an *S ligand* rather than as an *N ligand*.

Two coordination modes are possible: η_1 through the lone pair on S and η_2 through the C=S π bond. In the case of the simplest thiourea, the interaction through the lone pair on S is 9 kcal/mol more stable since the π^*_{CS} orbital is rather high in energy and cannot interact efficiently. Electron-withdrawing or -donating substituents attached to the phenyl ring considerably modify the energy levels of the lone pairs and of the π^*_{CS} orbital, despite the distance between these substituents and the C=S bond. The conjugation of the entire molecule allows the acceptor or donor effect to be propagated over this rather long distance.

Since the energy difference between the η_1 and η_2 coordination modes is small, it is most probable that the considerable stabilization of the π^*_{CS} orbital by electron-withdrawing substituents will result in a change of the coordination mode of the molecule in favor of the η_2 mode. This significant structural change could explain the strong decrease seen in the enantioselectivity. The influence of a donor group is much smaller.

The actual ligand is a dithiourea, possessing two sulfur atoms. Binding of this ligand to the metal ion through both sulfur atoms in an η_1 geometry would require the formation of a nine-membered ring, which is far from favorable. Much stronger interaction could be expected with ligands allowing the formation of smaller rings, for example with a dithiourea in which the nitrogen atoms are directly linked to one another.

The results presented here are qualitative but give a good interpretation of the experimental results, especially the variation in the enantiomeric excess. They will be completed in the future by calculations on more realistic ligands, in particular on dithioureas.

Experimental Section

General: All commercially available products were used without further purification. Conversions and enantiomeric excesses (*ee* values) were monitored by gas chromatography using a CYDEX B chiral column. − ^{1}H and ^{13}C NMR spectra were recorded with a Bruker-AM200 FT spectrometer with $CDCl_3$ as the solvent. Chemical shifts are reported in parts per million (ppm) and coupling constants are reported in Hertz (Hz). − All reactions were performed in screw-top V-Vials (Aldrich Z11,515−0). − (1*R*,2*R*)-(+)-*N*,*N*′-Dimethyl-1,2-diphenyl-1,2-ethanediamine was synthesized according to the previously described method of Mangeney et al.[7]

Ligand 2: Isolated yield 71%; white powder, m.p. 265 °C; $[\alpha]_D^{25}$ = −380 (*c* = 3.3, $CHCl_3$). − ^{1}H NMR: δ = 2.22 (s, 6 H, Ar-CH_3), 2.31 (s, 6 H, Ar-CH_3), 3.20 (s, 6 H, CH_3N), 7.13−7.31 (m, 12 H, Ar-H), 7.62−7.66 (m, 4 H, Ar-H), 8.13 (s, 2 H, NH). − ^{13}C NMR: δ = 18.5 (CH_3), 18.6 (CH_3), 33.5 (CH_3N), 60.9 (CH), 127.9−128.7 (C-Ar), 136.2, 136.4, 137.1, 137.2 (4Cq), 182.6 (CS). − IR: $\tilde{\nu}$ = 3373, 2947, 2919, 1498, 1479, 1453, 1333, 1291, 1228, 1095, 778, 700 cm^{-1}. − $C_{34}H_{38}N_4S_2$ (566.82): calcd. C 72.05, H 6.76, N 9.89, S 11.29; found C 72.17, H 7.04, N 9.84, S 11.15.

Ligand 3: Isolated yield 43%; powder, m.p. 125 °C; $[\alpha]_D^{25}$ = −455 (*c* = 3.1, $CHCl_3$). − ^{1}H NMR: δ = 3.19 (s, 6 H, CH_3N), 7.25−7.65 (m, 20 H, Ar-H + NCHPh), 7.76 (s, 2 H, NH). − ^{13}C NMR: δ = 34.7 (CH_3N), 61.4 (CH), 124.7−125.7 (C-Ar), 125.8−127.5 (CF_3), 128.3−130.1 (C-Ar), 135.2, 136.5 (2Cq), 142.7 (CNH), 182.3 (CS). − IR: $\tilde{\nu}$ = 3423, 3300, 3062, 3031, 2934, 1615, 1526, 1455, 1323, 1231, 1166, 1121, 1067, 838, 700 cm^{-1}. − $C_{32}H_{28}F_6N_4S_2$ (646.71): calcd. C 59.43, H 4.37, F 17.64, N 8.67, S 9.90; found C 57.75, H 4.40, F 16.05, N 7.86, S 7.52.

Ligand 4: Isolated yield 96%; powder, m.p. 157 °C; $[\alpha]_D^{25}$ = −655 (*c* = 3.2, $CHCl_3$). − ^{1}H NMR: δ = 3.22 (s, 6 H, CH_3N), 7.21−7.44 (m, 8 H, Ar-H), 7.53−7.69 (m, 10 H, Ar-H), 7.76 (s, 2 H, NH), 7.77 (s, 2 H, NCHPh). − ^{13}C NMR: δ = 34.8 (CH_3N), 60.9 (CH), 107.4 (CCN), 118.9 (CN), 124.1−132.6 (C-Ar), 136.4 (Cq), 144.1 (CNH), 181.8 (CS). − IR: $\tilde{\nu}$ = 3304, 3029, 2927, 2227, 1604, 1515, 1476, 1453, 1378, 1317, 1231, 1177, 1073, 834, 700 cm^{-1}. − $C_{32}H_{28}N_6S_2$ (560.73): calcd. C 68.55, H 5.04, N 15.00, S 11.41; found C 68.96, H 5.30, N 14.18, S 8.68.

Ligand 5: Isolated yield 11%; powder, m.p. 192 °C; $[\alpha]_D^{25}$ = −744 (*c* = 3, $CHCl_3$). − ^{1}H NMR: δ = 3.22 (s, 6 H, CH_3N), 7.19−7.32 (m, 6 H, Ar-H), 7.35−7.63 (m, 10 H, Ar-H + NCHPh), 7.74 (s, 2

H, NH), 8.12−8.19 (m, 4 H, Ar-H). − ^{13}C NMR: δ = 34.9 (CH_3N), 61.5 (CH), 121.6−129.4 (C-Ar), 136.2, 144.2, 145.6 (3Cq), 182.0 (CS). − IR: ṽ = 3628, 3341, 3059, 2936, 1596, 1565, 1548, 1509, 1318, 1236, 1111, 1078, 854, 706 cm^{-1}. − FAB calcd. for $C_{30}H_{28}N_6O_4S_2$ + H (600.71) 601.1691724; found 601.1717000.

Ligand 6: Isolated yield 87%; powder, m.p. 128 °C; $[\alpha]_D^{25}$ = −480 (c = 3.2, $CHCl_3$). − ^{1}H NMR: δ = 3.08 (s, 6 H, CH_3N), 3.74 (s, 6 H, OCH_3), 6.79−6.84 (m, 4 H, Ar-H), 7.11−7.20 (m, 12 H, Ar-H + NCHPh), 7.43−7.47 (m, 4 H, Ar-H), 7.79 (s, 2 H, NH). − ^{13}C NMR: δ = 34.2 (CH_3N), 55.5 (OCH_3), 61.2 (CH), 113.9 (C-Ar), 127.9−129.2 (C-Ar), 132.6 (Cq), 137.1 (CNH), 157.9 (OCq), 183.1 (CS). − IR: ṽ = 3347, 3029, 2933, 2834, 1610, 1514, 1478, 1464, 1336, 1242, 1179, 1075, 1032, 829, 753, 701 cm^{-1}. − $C_{32}H_{34}N_4O_2S_2$ (570.77): calcd. C 67.34, H 6.00, N 9.82, S 11.23; found C 66.96, H 5.99, N 9.47, S 10.67.

Ligand 7: Isolated yield 80%; powder, m.p. 130 °C; $[\alpha]_D^{25}$ = −343 (c = 3, $CHCl_3$). − ^{1}H NMR: δ = 3.16 (s, 6 H, CH_3N), 3.72 (s, 6 H, OCH_3), 3.80 (s, 6 H, OCH_3), 7.02−7.65 (m, 18 H, Ar-H + NCHPh), 7.98 (s, 2 H, NH). − ^{13}C NMR: δ = 33.7 (CH_3N), 55.5 (OCH_3), 55.6 (OCH_3), 60.6 (CH), 122.1 (Cq) 126.7−129.5 (C-Ar), 137.2 (Cq), 152.5 (OCq), 158.1 (OCq), 182.2 (CS). − IR: ṽ = 3393, 3345, 3036, 2958, 2939, 2835, 2120, 2048, 1614, 1517, 1454, 1342, 1313, 1283, 1208, 1158, 1034, 830, 701 cm^{-1}. − $C_{34}H_{38}N_4O_4S_2$ (630.82): calcd. C 64.74, H 6.07, N 8.88, S 10.16; found C 63.42, H 5.95, N 8.60, S 10.03.

Ligand 8: Isolated yield 78%; powder, m.p. 220 °C; $[\alpha]_D^{25}$ = −490 (c = 3.1, $CHCl_3$). − ^{1}H NMR: δ = 3.18 (s, 6 H, CH_3N), 3.76 (s, 12 H, OCH_3), 3.81 (s, 6 H, OCH_3), 6.69−7.53 (m, 16 H, ArH + NCHPh), 7.79 (s, 2 H, NH). − ^{13}C NMR: δ = 34.4 (CH_3N), 56.2 (2 OCH_3), 60.9 (OCH_3), 61.1 (CH), 102.7 (C-Ar), 128.0−129.5 (C-Ar), 135.2, 135.8, 136.8, 152.9 (4 Cq), 181.8 (CS). − IR: ṽ = 3336, 2939, 2839, 1599, 1533, 1509, 1481, 1465, 1433, 1337, 1313, 1233, 1132, 1077, 1006, 700 cm^{-1}. − $C_{36}H_{42}N_4O_6S_2$ (690.87): calcd. C 62.59, H 6.13, N 8.11, S 9.28; found C 62.56, H 5.88, N 7.99, S 8.15.

Ligand 9: Isolated yield 79%; powder, m.p. 143 °C; $[\alpha]_D^{25}$ = −433 (c = 3.2, $CHCl_3$). − ^{1}H NMR: δ = 2.97 [s, 12 H, $N(CH_3)_2$], 3.16 (s, 6 H, CS−CH_3N), 6.74−7.59 (m, 20 H, Ar-H + NCHPh), 7.91 (s, 2 H, NH). − ^{13}C NMR: δ = 34.1 (CH_3NCS), 41.0 [$N(CH_3)_2$], 61.2 (CH), 125.6−129.7 (C-Ar), 137.2 (Cq), 183.2 (CS). − IR: ṽ = 3363, 3281, 3030, 2941, 2886, 2799, 1613, 1524, 1334, 1231, 1164, 1074, 944, 817, 735, 700 cm^{-1}. − $C_{34}H_{40}N_6S_2$ (596.85): calcd. C 68.42, H 6.76, N 14.09, S 10.72; found C 67.51, H 6.77, N 13.84, S 10.65.

Typical Procedure for the Reduction of Ketones: $[RhCl(COD)]_2$ (1.6 mg, 6.36×10^{-3} mmol Rh) and 3 equiv. of dithiourea were mixed in 2 mL of a solution of potassium *tert*-butoxide in 2-propanol {12×10^{-3} mmol L^{-1}; [*t*BuOK]/[Rh] = 4}. After stirring for 1.5 h at room temperature under argon, the ketone (0.12 mmol) was added. The resulting mixture was stirred for a further 15 h at room temperature and then heated to 70 °C. The reaction was monitored by GC.

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Received September 20, 2000
[O00492]