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Thioureas as new chiral ligands for the asymmetric hydroformylation of styrene with rhodium(I) catalysts

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Abstract

Various new chiral thioureas have been synthesized and used as ligands for the asymmetric hydroformylation of styrene catalyzed by rhodium(I) complexes. The best results were obtained with *N*-phenyl-*N′*-(*S*)-(1-phenylethyl)-thiourea associated to a cationic rhodium(I) precursor, and asymmetric induction of 40% was then achieved. As enantioselectivity is obtained with low conversions, various parameters have been examined in order to increase the catalytic activity without the loss of asymmetric induction. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Asymmetric catalysis; Enantioselective hydroformylation; Rhodium(I); Styrene; Chiral thioureas

1. Introduction

The challenge of asymmetric hydroformylation is not only related to enantioselectivity, but also to chemoselectivity (hydroformylation vs. hydrogenation) and regioselectivity [branched (b) vs. normal (n) aldehyde] [1–4]. The hydroformylation of vinyl aromatics leads mainly to the branched aldehydes, which can be further oxidized to corresponding acids. These compounds are effective nonsteroidal analgesics [5,6]. 2-Phenylpropionic acid is the simplest member of the family of 2-arylpropionoic acids, and there has been much interest in asymmetric hydroformylation of styrene [1–4]. Generally, platinum complexes with P,P ligands give high enantiomeric excess (ee) provided that tin(II) chloride is added, but give low reaction rate and chemoselectivity. Rhodium(I) complexes with chelating P,P ligands give higher activity, chemo- and regioselectivity with moderate enantioselectivity. [1–4,7] However, good enantioselectivities have recently been reported with chiral diphosphite (90% ee) [8,9] or phosphine–phosphite (94% ee) [10–12] ligands.

If chiral phosphorus ligands are widely used in catalysis, most of them are air-sensitive and their synthesis is rather tedious. Thus, there is a strong demand for more stable and easy accessible chiral ligands, such as sulfur- or nitrogen-containing ligands. Chiral dithiolates [2,13,14]

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have been used in the asymmetric hydroformylation of styrene, but low enantioselectivities have been obtained in the absence of added chiral phosphorus ligands.

As part of our efforts to develop new chiral nitrogen ligands [15], our laboratory has initially studied chiral dithioureas [16] for the hydride transfer reduction of prochiral ketones with isopropanol, giving rise to optically active secondary alcohols. Competitive or even better results than with other systems [16 and references cited therein] were gathered with rhodium, iridium and ruthenium. Rhodium(I) complexes with nonchiral thioureas have already been used in hydroformylation of styrene [17,18], which prompted us to examine this reaction with their chiral analogs.

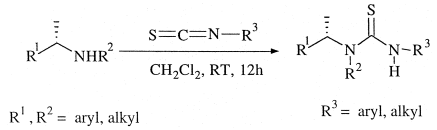
We report, in the present paper, the synthesis of new chiral mono-, acyl- or dithioureas. These molecules show good stability, easy accessibility and accept large structure modifications. The catalytic activity of the systems formed by the addition of these ligands to cationic rhodium(I) precursors in the asymmetric hydroformylation of styrene is reported, as well as a brief structure–activity relationship.

2. Results and discussion

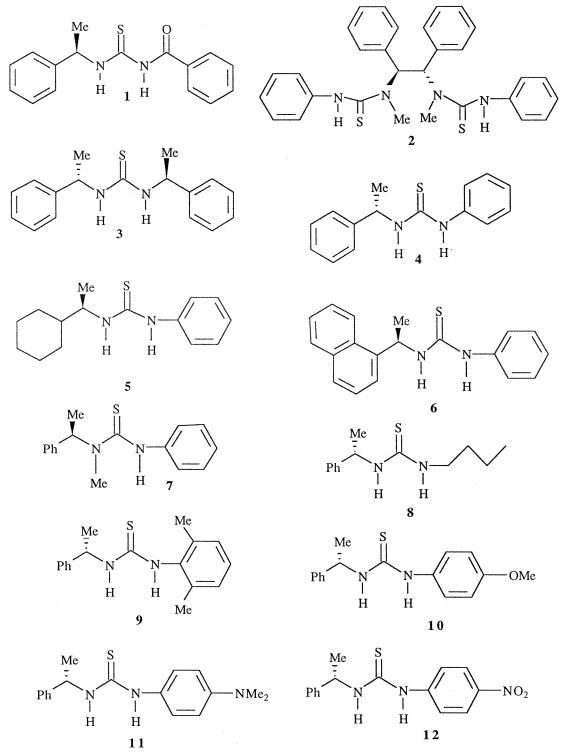
2.1. Ligand synthesis

Thioureas are easily synthesized by reaction of chiral amines with stoichiometric amounts of isothiocyanates (Scheme 1). The purified monothioureas are always obtained with good yields (> 70%) (see Section 4).

Scheme 2 describes all the thioureas synthesized in this work.



Scheme 1.

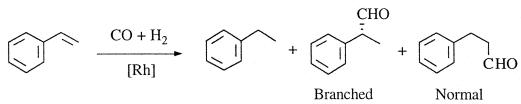


Scheme 2.

This library of ligands embraces examples of acylthiourea **1**, dithiourea **2**, C_2-symmetric monothiourea **3** and a series of disymmetric monothioureas **4–12** bearing various substituents on each nitrogen atom which allow us to study electronic and steric effects on catalytic activity.

2.2. Catalytic hydroformylation of styrene

Neutral $[Rh(cod)Cl]_2$ or cationic $[Rh(cod)_2]$-BF_4 complex [cod = cycloocta-1,5-diene] without additional ligand efficiently catalyzes the hydroformylation of styrene, leading mainly to the branched product (b:n > 90:10) (Scheme 3) [1–4,19].



Scheme 3.

In order to get a blank reaction and to evaluate the ligand effects, we studied these complexes in standard hydroformylation conditions ([Rh] = 5.10^{-5} mol, styrene/Rh = 50, toluene = 10 ml, CO + H_2(1:1) = 40 bar, T = 40°C, t = 24 h) [1–4]. [Rh(cod)$_2$]BF_4 gives total conversion with 95% selectivity to the aldehyde (5% hydrogenation) and 94% selectivity to the branched isomer. [Rh(cod)Cl]$_2$ is slightly less active and regioselective.

2.2.1. Influence of the chiral ligand on the hydroformylation of styrene

Various combinations of ligands (L^*) **1–12** with rhodium complexes were used as catalysts for the asymmetric hydroformylation of styrene.

Although thiourea ligands form inactive systems with [Rh(cod)Cl]$_2$ as catalyst precursor, in standard conditions (40°C, 40 bar CO + H_2 at 1:1), the cationic rhodium complex [Rh(cod)$_2$]BF_4 combined with these ligands shows activity: selected results are reported in Table 1. Enantioselectivity requires one to six equivalents of diphosphine per metal and increasing the ligand to metal ratio allows higher ee but lower activity [1–4]. Thus, one to five equivalents of thiourea ligands were added to the cationic rhodium precursor.

Table 1
Asymmetric hydroformylation of styrene with [Rh(cod)$_2$]BF_4 in the presence of thiourea
Conditions: [Rh(cod)$_2$]BF_4 = 5.10^{-5} mol; toluene = 10 ml; styrene/L^*/Rh = 350:1:1, CO + H_2 (1:1) = 40 bar, T = 40°C, t = 18 h.

Entry	L^*	% Conversion	% Aldehyde	b/n	% ee
1	**1**	4	87	92:8	n.d.
2	**2**	3	94	82:18	n.d.
3	**3**	88	99	92:8	0
4[a]	**3**	18	99	85:15	16 (−)
5	**4**	18	98	91:9	24 (−)
6[b]	**4**	100	100	91:9	1 (−)
7	**5**	74	100	88:12	0
8	**6**	56	99	92:8	11 (−)
9	**7**	55	99	93:7	2 (−)
10	**8**	75	99	92:8	2 (−)
11	**9**	67	100	91:9	2 (−)
12	**10**	66	100	93:7	5 (−)
13	**11**	61	99	85:15	7 (−)
14	**12**	30	99	93:7	1 (−)

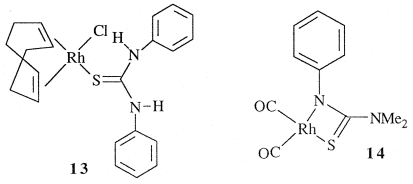
[a] L^*:Rh = 2:1.
[b] t = 96 h.

Cauzzi et al. [17,18] showed that acylthioureas are efficient ligands for the rhodium catalyzed hydroformylation of styrene. Then we examined their chiral analog **1** [20] (entry 1, Table 1). This system gives low conversion, and induces up to 13% of hydrogenation product.

C_2-symmetric dithiourea **2**, described in ruthenium-catalyzed hydride transfer reduction of acetophenone [16], were tried for the hydroformylation of styrene (entry 2, Table 1). The conversion is low, even at long reaction time (96 h). More severe conditions (80°C) lead to low ee values (< 5%).

All the other substrates are chiral monothioureas differing by their structure. Comparison of monothioureas **3** [21] and **4** (Scheme 2) show that the C_2 axis is nonessential for asymmetry contrary to P,P chelating ligands. Very good conversion, chemo- and regioselectivities are obtained with **3**, but without any asymmetric induction (entry 3, Table 1). These results suggest that coordination of this ligand on the metal center does not proceed. Chemo- and regioselectivities are very good with **4**, and enantioselectivity of 24% ee is achieved (entry 5, Table 1). This is, to our knowledge, the best result obtained with complexes containing only sulfur ligands. However, when the reaction time is long enough to ensure complete conversion of styrene (96 h), the enantioselectivity is lost (1% ee), although the same chemo- and regioselectivities are observed. Racemization of the optically active aldehyde may occur [1–4], but can be avoided by preparing in situ its non-racemizable diethylacetal [22]. However, no conversion was obtained using triethylorthoformate with our system. Evolution of the active species is to be taken into account and longer reaction times probably afford the hydrido rhodium carbonyl unmodified species.

The influence of the chiral amino group, both on the activity and the enantioselectivity was



Scheme 4.

examined (ligands **5**–**7**, entries 7–9, Table 1). Both conversion and chemoselectivity are good with these rhodium-ligand systems. Ligands **5** and **7** are not selective while **6** gives 11% ee. This enantioselectivity is similar to the one obtained with DIOP [1–4]. Since enantioselectivity is better with aryl substituents (4 and 6), $\pi-\pi$ interactions between the ligand and the substrate may better point out the way of approaching the metallic center. The hydrogen atom, on the nitrogen atom of the chiral moiety, is necessary for the enantioselectivity. This suggests that this nitrogen atom is bound to the metal center in the case of ligand **4**, and cannot coordinate in the case of ligand **7**. The nitrogen atom of the achiral moiety may then coordinate to the metal center.

We also studied the influence of the nonchiral group on the selectivities with the best chiral moiety (ligands **8**–**12**, entries 10–14, Table 1), since basicity and steric or electronic effects on the achiral moiety can direct the coordination in a preferential way. Ligands **8**, **9**, **10**, or ,**11** give similar results: conversion is good, but with poor ee values (2–7%). Ligand **12**, with an electron withdrawing group in para position (Scheme 2) gives lower conversion and no ee (entry 14, Table 1).

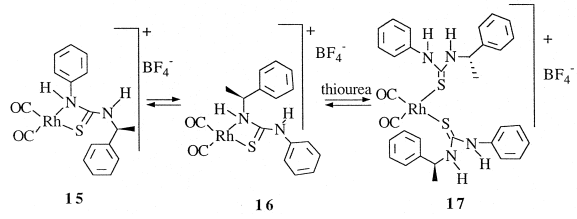
In summary, monothioureas associated with cationic rhodium(I) precursor are moderate to active systems for the hydroformylation of styrene in standard conditions, leading to excellent chemoselectivity ($\geq 98\%$), good regioselectivity ($\geq 85\%$) but enantioselectivity below 5%, except for ligands **4**, **6**, and **11**. An excess of ligands **4**–**12** (i.e., $L^*/Rh = 2{:}1$ and more) inhibits hydroformylation whereas with a **3**/Rh ratio of 2, conversion goes down to 18% and ee up to 16%, with good chemo- and regioselectivities (entry 3, Table 1). The reaction does not work when a larger excess of **3** is used.

The results of the catalytic runs in standard conditions suggest the presence of more than one catalytic active species. Monothiourea ligands possess three potential coordinating sites: the sulfur atom and the two nitrogen atoms. The sulfur atom is the preferred site which has been demonstrated by Cauzzi et al. [17,18] with an X-ray crystal structure of the chlorodicarbonyl(thiourea) rhodium complex (**13**, Scheme 4) [20,21].

However, monothiourea can act as monodentate N or S ligand or bidentate N,S chelating or bridging ligand. Besides, each N atom may be bound to the metallic center. Formation of a four-membered ring (**14**, Scheme 4) has already been reported [23]. All these possibilities show that the coordination chemistry of such chiral thioureas is quite complex and hardly described in the literature.

In the cationic complex $[Rh(cod)_2]BF_4$, clivage of one cod ligand creates two vacant coordination sites which can be occupied by the sulfur atom and by the forced coordination of one of the nitrogen atoms (**15** or **16**, Scheme 5).

Examination of the ^1H NMR spectrum of the thiourea **4** with $[Rh(cod)_2]BF_4$ shows displacement of one cod ligand by the thiourea. Moreover, the proton signal of the PhNH– group ($\delta = 7.75$: free ligand) is shifted downfield at $\delta = 11.48$, while the peak of the other –NH– group ($\delta = 6.60$) is shifted upfield at $\delta = 5.96$. Examination of the IR spectrum also shows



Scheme 5.

displacement of the N–H stretching bands ν (cm^{-1}): from 3355, 3336, and 3252 in the free ligand to 3332 and 3220 (broad) in the complex. This is consistent with the coordination of at least one nitrogen atom to the metallic center. The preferential coordination of the nitrogen atom of the chiral moiety might afford the most efficient species for asymmetric induction. If the two nitrogen sites offer very different basicity or steric bulkiness, one of them may thus be favored for coordination.

Potentially bidentate S,S ligand **1** and S,O ligand **2** give inactive systems with rhodium. These results must be compared with the inactivity observed for monothioureas **3**–**12** used in excess: we can deduce that the coordination of two soft sulfur sites on the metallic center creates very stable but inactive species (**17**, Scheme 5).

2.2.2. Influence of various parameters

As ligand **4** appears to be the best candidate for enantioselective hydroformylation, it has been chosen to examine the role of several parameters, namely solvent, temperature, CO and H_2 pressures in order to define the best conditions.

Table 2 summarizes the influence of the solvent on the reaction. Since low polar solvents are more effective [1–4], toluene and heptane were tested. More polar solvents like tetrahydrofuran (THF), dichloromethane or acetone induce an increase in rhodium concentration, because the cationic precursor is only slightly soluble in nonpolar solvents, contrary to the ligand.

When a **4**/Rh ratio of 1 is used, styrene is hardly transformed either in acetone or in dichloromethane. Longer reaction time gives only low conversions (entries 1 and 2, Table 2). THF is known to decrease both enantioselectivity and activity of rhodium complexes with P,P ligands [1–4]. Inversely with thioureas, THF allows high conversion, but poor ee (entry 5, Table 2) and metallic particles of rhodium are observed. Toluene proves to be convenient for this reaction (entry 6, Table 2), and heptane leads to higher enantioselectivity (entry 7, Table 2) but lower conversion, because rhodium precursor and ligand are poorly soluble even at 40°C. Enantioselectivity increases and activity decreases while the polarity of the solvent diminishes. For all experiments in low polar solvents, traces of yellow-orange precipitate were found on the walls of the vessel in the autoclave (see Section 4). This solid is insoluble in common solvents and is identified by IR as a dicarbonylrhodium species ($\nu = 2064$ and 2026 cm^{-1}) without thiourea nor cyclooctadiene ligand. Finally, with **4**/Rh ratio of 2, polar solvents favor the activity (entries 2 and 4, Table 5) and with 5 equivalents of **4** per metal, activity is lost.

At this point, the effects of temperature and total pressure were examined. Selected results are reported in Table 3.

Table 2
Hydroformylation of styrene by $[Rh(cod)_2]BF_4$ with thiourea **4**: solvent effects
Conditions: $[Rh(cod)_2]BF_4 = 5.10^{-5}$ mol; toluene = 10 ml; styrene/**4**/Rh = 350:1:1, CO + H_2 (1:1) = 40 bar, $T = 40$°C, $t = 18$ h.

Entry	Solvent (ε)	L/Rh	% Conversion	% Aldehyde	b/n	% ee
1	Acetone (20.7)	1:1	21[a]	100	92:8	0
2	Acetone (20.7)	2:1	9[a]	100	94:6	0
3	CH_2Cl_2 (9.1)	1:1	2[a]	100	n.d.	n.d.
4	CH_2Cl_2 (9.1)	2:1	38[a]	100	93:7	6 (−)
5	THF (7.4)	1:1	60	100	88:12	7 (−)
6	Toluene (2.4)	1:1	18	98	91:9	24 (−)
7	Heptane (1.9)	1:1	7	92	93:7	41 (−)

[a] $t = 96$ h.

Chemoselectivity is excellent (hydrogenation $< 1\%$). Increasing the pressure decreases the enantioselectivity (from 24% to 2–4%), although good conversions are observed. Moreover, the linear isomer is formed in greater quantities at high temperature. Arena et al. [24] observed that phosphine ligands may be displaced by CO. Similarly, high total pressure favors the release of the thiourea ligand, and then the formation of active (but not enantioselective) hydridocarbonylrhodium species, which explain the loss of asymmetric induction. The temperature exhibits only small effect on the enantioselectivity in the range under study. Table 7 shows that higher total pressures give better conversions and lower enantioselectivities, and the highest ee is obtained for the lowest total pressure examined.

Increasing the partial pressure of dihydrogen (p_{H_2}) gives better activity with platinum systems [1,25] and sometimes better enantioselectivity [1–4]. A high partial pressure of carbon monoxide (p_{CO}) is generally considered as an inhibitor for the hydroformylation reaction. Many research groups reported that high p_{CO} values bring out low reaction rates and low optical purity for the aldehyde [1–4]. Several different catalytic species might be operative, and their relative concentrations depend on the p_{CO} values. Table 4 summarizes the effects of p_{CO} and p_{H_2} on the activity and the selectivities of the reaction.

Enantioselectivity was not measured for conversions below 5%. From 10 to 20 bar of CO, with a constant total pressure of 40 bar, both activity and enantioselectivity (12% ee at p_{CO} of 13 bar) increase quite linearly, up to a maximum of 20 bar of each gas (24% ee) (Table 4). Highest enantioselectivity and activity are obtained for a CO/H_2 ratio of 1. Above this value, inhibition is observed, as expected.

Table 3
Hydroformylation of styrene by cationic rhodium complexes with thiourea **4**: temperature and pressure effects
$[Rh(cod)_2]BF_4 = 5.10^{-5}$ mol; toluene = 10 ml; styrene/**4**/Rh = 350:1:1, $CO + H_2$ (1:1) = 40 bar, $T = 40°C$, $t = 18$ h.

Entry	T (°C)	p_{CO}/p_{H_2} (bar)	% Conversion	% Aldehyde	b/n	% ee
1	50	30:30	90	100	88:12	4 (−)
2	80	30:30	80	99	58:42	3 (−)
3	50	40:40	100	99	94:6	2 (−)

Table 4
Effect of CO partial pressure in the asymmetric hydroformylation of styrene
$[Rh(cod)_2]BF_4 = 5.10^{-5}$ mol, styrene/**4**/Rh = 300:1:1, toluene = 10 ml, $T = 40°C$, $t = 18$ h.

Entry	p_{CO}	p_{H_2}	% Conversion	% Aldehyde	b/n
1	10	30	2	83	94:6
2	13	27	8	100	94:6
3	20	20	18	98	91:9
4	25	15	4	95	95:5
5	27	13	4	97	96:4
6	30	10	3	100	94:6

3. Conclusion

We demonstrate in this paper that chiral monothioureas are easy to synthesize, air-stable and can be combined with rhodium precursors in order to induce asymmetry in the catalytic hydroformylation of styrene, in mild conditions. Such a result offers, to our knowledge, the first example of significant enantioselectivity in this reaction without any phosphorus ligand. Till now, conversion of styrene and ee are modest, even if ee value up to 40% is obtained in heptane. The study of various parameters allowed us to determine that low temperature and moderate pressure (40°C, 40 bar $CO + H_2$) are required to observe asymmetry. The ligand/rhodium ratio is critical, since any activity is lost for 2 equivalents of thiourea per metal. If the sulfur atom is the preferred coordination site of thiourea, the binding of one of the nitrogen atoms of the ligand can be forced in cationic species. Such chelated complex has already been prepared [23]. This bidentate coordination must be the key to the asymmetric induction, as for

P,P ligands. The coordination behavior of thiourea ligands with rhodium is under study and will be reported later.

4. Experimental

4.1. Materials

All the organic and organometallic reagents are pure commercial products. The solvents are reagent grade and are dried and distilled by standard techniques before use. All manipulations of rhodium compounds are carried out under argon by means of standard Schlenk-tube techniques.

Melting points (m.p.), noncorrected, are determined with an Electrothermal 9100 apparatus. Elemental analysis (C,H,N) are obtained from the Service Central d'Analyse of the CNRS (Solaize). IR spectra (KBr pellets) are recorded on an FT Bruker Vektor 22 spectrometer. ^{1}H and ^{13}C NMR spectra are obtained with a Bruker AC-100 instrument (^{1}H 100 MHz, ^{13}C 25 MHz: δ (ppm), J (Hz), s: singlet, d: doublet, t: triplet, q: quadruplet, m: multiplet, br: broad). Analytical GLC is carried out with an Intersmat chromatograph fitted with a 15-m EC-5 (SE-54) capillary column. Analytical HPLC is carried out with a Shimadzu LC-10AS chromatograph equipped with a chiral column (CHIRALCEL-OD). Rotatory powers are determined with a Perkin-Elmer 241 polarimeter ($l = 1$ dm; 25°C; concentration in g/dm^3).

4.2. Syntheses

$[Rh(cod)Cl]_2$ [26], $[Rh(cod)_2]BF_4$ [27] [cod = cycloocta-1,5-diene] are prepared according to the literature. (*R,R*)-(−)-*N,N′*-dimethyl-1,2-diphenyl-1,2-ethylenediamine has been synthesized according to the procedure described by Alexakis et al. [28,29]. Synthesis and characterization of (*R,R*)-(−)-*N,N′*-dimethyl-1,2-diphenyl-1,2-ethylenyl-diphenyldithiourea (**2**) [30], (+)-(*S,S*)-*N,N′*-bis(1-phenylethyl)thiourea (**3**) [21] have already been described elsewhere.

4.2.1. General procedure for the synthesis of monothioureas

The chiral amine is added to a stoichiometric amount of the isothiocyanate (5–10 mmol) in 10 ml of dichloromethane. The reaction takes place overnight at room temperature (an inert atmosphere is not necessary). The solution is then poured into 75 ml of pentane. The precipitate is collected with a Millipore filtration system, washed with several portions of pentane and dried under vacuum. If no precipitate forms, the solution is percolated through a small bed of silica and the solvent is evaporated.

4.2.2. Spectroscopic data

*4.2.2.1. (+)-N-(S)-(1-phenylethyl)-N′-phenylacylthiourea (**1**) [20].* M.W.: 284.376. Yield 98%. Viscous oil. Analysis: Found (calc. for $C_{16}H_{16}N_2OS$) C, 67.54 (67.58); H 5.94 (5.67); N 9.54 (9.85). FT-IR (KBr) (cm^{-1}): 3350, 3238 (NH), 3030, 2975, 2928, 2860 (CH), 1671 (C═O), 1537 (C═S), 1336, 1260, 1165, 1078, 1025, 1001, 962, 911, 699, 602. ^{1}H NMR ($CDCl_3$) δ: 11.2 (d,1H, $^{3}J_{HH} = 7.5$, NHCO–); 7.9–7.2 (m, 10H, arom.); 6.0–5.5 (qd, 1H, $^{3}J_{HH} = 7.5$, $^{3}J_{HH} = 7.0$, CH); 1.63 (d, 3H, $^{3}J_{HH} = 6.9$, CH_3). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$) δ: 178.7 (CS); 166.9 (CO); 141.5–133.2 (Carom.); 128.7–127.4–126.1 (CHarom.); 54.9 (CH); 21.4 (CH_3). $[\alpha]_D = +8$ ($c = 5.02$, $CHCl_3$).

*4.2.2.2. (+)-N-(S)-1-phenylethyl-N′-phenylthiourea (**4**) [20].* M.W.: 256.365. Yield 93%, m.p. 62–63°C. Analysis: Found (calc. for $C_{15}H_{16}N_2S$) C, 70.38 (70.28); H 6.29 (6.29); N 10.75 (10.93). FT-IR (KBr) (cm^{-1}): 3355, 3336, 3252 (NH), 3084, 3058, 3027, 2980, 2971, 2959, 2923, 2865 (CH), 1591 (C═S), 1534, 1495, 1454, 1384, 1356, 1310, 1295, 1237, 1198, 1084, 1022, 759, 696, 642, 602. ^{1}H NMR ($CDCl_3$) δ: 7.75 (s, 1H, NHPh); 7.7–7.1 (m,

10H, arom.); 6.6 (br d, 1H, $^3J_{HH}$ = 7.6, NH); 5,65 (qd, 1H, $^3J_{HH}$ = 7.6, $^3J_{HH}$ = 6.8, CH); 1,52 (d, 3H, $^3J_{HH}$ = 6.8, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ: 180.0 (CS); 142.5–136.4 (Carom.); 130.5–129.1–127.9–127.5–126.4–125.4 (CHarom.); 54.7 (CH); 21.8 (CH_3). $[\alpha]_D$ = +92 (c = 5.08, $CHCl_3$).

*4.2.2.3. (−)-N-(R)-(1-cyclohexylethyl)-N′-phenyl-thiourea (**5**).* M.W.: 262.413. Yield: 88%, m.p.: 118–119°C. Analysis: Found (calc. for $C_{15}H_{22}N_2S$) C 68.68 (68.66); H 8.39 (8.45); N 10.74 (10.68). FT-IR (KBr) (cm^{-1}): 3235–3145 (NH), 3050, 2922, 2851 (CH), 1599,1552 (C = S), 1497, 1449, 1352, 1314, 1259, 750, 700. ^1H NMR ($CDCl_3$) δ: 7.95 (s, 1H, NHPh); 7.5–7.1 (m, 5H, arom.); 5.9 (br d, 1H, $^3J_{HH}$ = 8.1, NH); 4.39 (m, 1H, CH); 1.8–0.8 (m, 14H, $^3J_{HH}$ = 6.7 CH_3, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ: 179.5 (CS); 136.0 (Carom.); 130.2–127.2–125.1 (CHarom.); 55.7 (CHNH); 42.8 (CH); 29.2–28.8–26.3–26.1 (CH_2); 17.2 (CH_3). $[\alpha]_D$ = −69 (c = 5.06, $CHCl_3$).

*4.2.2.4. (−)-N-(R)-(1-(1-naphtyl)ethyl)-N′-phenyl-thiourea (**6**).* M.W.: 306.425. Yield: 81%, m.p.: 96–97°C. Analysis: Found (calc. for $C_{19}H_{18}N_2S$) C 74.37 (74.47); H 5.88 (5.92); N 9.20 (9.14). FT-IR (KBr) (cm^{-1}): 3401, 3290, 3237 (NH), 3043, 3029, 2958, 2930, 2872 (CH), 1592, 1529 (C═S), 1451, 1372, 1315, 1240, 1130, 789, 772, 695. ^1H NMR ($CDCl_3$) δ: 8.5 (br s, 1H, NHPh); 8.5–7.0 (M, 12H, arom.); 6.5–6.2 (M, 2H, CH, NH); 1.76 (d, 3H, $^3J_{HH}$ = 6.4, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ: 179.3 (CS); 137.4–136.3–134.0–131.3 (Carom.); 130.1–128.8–128.7–127.0–126.9–126.1–125.2–124.9–123.8–123.0 (CHarom.); 51.0 (CH); 20.2 (CH_3). $[\alpha]_D$ = −127 (c = 5.06, $CHCl_3$).

*4.2.2.5. (+)-N-methyl-N-(R)-1-phenylethyl-N′-phenyl-thiourea (**7**).* M.W.: 270.392. Yield: 97%, m.p.: 133–134°C. Analysis: Found (calc. for $C_{16}H_{18}N_2S$) C 71.20 (71.07); H 6.69 (6.71); N 10.22 (10.36). FT-IR (KBr) (cm^{-1}): 3335 (NH), 2932 (CH), 1594, 1522 (C═S), 1494, 1453, 1378, 1320, 1285, 1250, 1200, 1094, 747, 695. ^1H NMR ($CDCl_3$) δ: 7.5–7.1 (M, 10H, arom.); 7.05 (br s, 1H, NH); 6.78 (q, 1H, $^3J_{HH}$ = 7.0, CH); 2.88 (s, 3H, NCH_3); 1,61 (d, 3H, $^3J_{HH}$ = 7.0, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ: 182.4 (CS); 140.1–139.9 (Carom.); 128.7–127.7–127.1–125.8–125.6 (CHarom.); 58.1 (CH); 32.5 (NCH_3); 15.8 (CH_3). $[\alpha]_D$ = +251 (c = 4.94, $CHCl_3$).

*4.2.2.6. (+)-N-(S)-1-phenylethyl-N′-butyl-thiourea (**8**) [20].* M.W.: 236.375. Yield: 100%. Oil. Analysis: Found (calc. for $C_{13}H_{20}N_2S$) C 65.99 (66.06); H 8.55 (8.53); N 11.58 (11.85). FT-IR (neat) (cm^{-1}): 3261 (NH), 3062, 2960, 2930, 2871 (CH), 1547 (C═S), 1451, 1349, 1216, 1077, 1029, 945, 760, 700. ^1H NMR ($CDCl_3$) δ: 7.3–7.1 (M, 5H, arom.); 6.91 (br s, 1H, NHBu); 6.13 (br l, 1H, NH); 5.0 (br s, 1H, CH); 3.3 (br s, 2H, NCH_2); 1.36 (d, 3H, $^3J_{HH}$ = 6.8, CH_3); 1.3–0.6 (M, 7H, $CH_2CH_2CH_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ: 180.2 (CS); 142.2 (Carom.); 128.4–127.1–125.5 (CHarom.); 53.3 (CH); 44.1 (NCH_2); 30.5 (CH_2); 22.6–19.4–13.3 (CH_2, CH_3). $[\alpha]_D$ = +27 (c = 6.14, $CHCl_3$).

*4.2.2.7. (+)-N-(S)-1-phenylethyl-N′-(o,o′-dimethyl)phenyl-thiourea (**9**).* M.W.: 284.419. Yield: 72%, m.p.: 129–130°C. Analysis: Found (calc. for $C_{17}H_{20}N_2S$) C 71.74 (71.79); H 6.98 (7.09); N 9.68 (9.85). FT-IR (KBr) (cm^{-1}): 3372–3356–3192 (NH), 3000, 2970 (CH), 1541 (C═S), 1498, 1446, 1371, 1269, 1245, 1083, 1024, 781, 705. ^1H NMR ($CDCl_3$) δ: 7.5 (br s,1H, NHPh); 7.3–7.1 (M, 8H, arom.); 5.7 (br s, 2H, NH, CH); 2.14 (br s, 6H, Me arom.); 1.45 (d, 3H, $^3J_{HH}$ = 7.0, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ: 180.1 (CS); 142.3–137.2 (Carom.); 128.9–128.6–127.4–126.0 (CHarom.); 53.7 (CH_3); 21.2–18.0 (CH_3). $[\alpha]_D$ = +57 (c = 5.10, $CHCl_3$).

*4.2.2.8. (+)-N-(S)-1-phenylethyl-N′-para-methoxyphenyl-thiourea (**10**) [20].* M.W.: 286.392. Yield: 83%, m.p.: 99–100°C. Analy-

sis: Found (calc. for $C_{16}H_{18}N_2OS$) C 67.11 (67.10); H 6.23 (6.34); N 9.71 (9.78). FT-IR (KBr) (cm^{-1}): 3362–3185 (NH), 2985, 2830 (CH), 1607 (C═S), 1513, 1418, 1377, 1299, 1283, 1162, 1101, 1034, 832, 792, 737, 695. ^1H NMR ($CDCl_3$) δ: 7.86 (br s,1H, NHPh); 7.3–6.7 (M, 9H, arom.); 6.6 (br d, 1H, $^3J_{HH} = 7.9$, NH); 5,63 (qd, 1H, $^3J_{HH} = 7.5$, $^3J_{HH} = 6.8$, CH); 3.76 (s, 3H, OMe); 1.47 (d, 3H, $^3J_{HH} = 6.8$, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ: 180.0 (CS); 159.0 (CO); 144.3–142.5 (Carom); 128.8–127.4–126.0 (CHarom); 55.4–54.0 (OMe, CH); 21.6 (CH_3). $[\alpha]_D = +115$ ($c = 5.06$, $CHCl_3$).

*4.2.2.9. (+)-N-(S)-1-phenylethyl-N′-(para-N″,N″-dimethyl)phenyl-thiourea: **(11)***. M.W.: 299.434. Yield: 96%, m.p.: 139–141°C. Analysis: Found (calc. for $C_{17}H_{21}N_3S$) C 68.13 (68.19); H 7.00 (7.07); N 13.94 (14.03). FT-IR (KBr) (cm^{-1}): 3361–3187 (NH), 3028, 2969, 2812 (CH), 1608 (C═S), 1527, 1447, 1371, 1299, 1283, 1170, 1022, 948, 845, 820, 786, 740, 695. ^1H NMR ($CDCl_3$) δ: 7.54 (br s,1H, NHPh); 7.3–6.5 (M, 9H, arom.); 6.0 (br d, 1H, $^3J_{HH} = 8.5$, NH); 5,63 (qd, 1H, $^3J_{HH} = 7.9$, $^3J_{HH} = 6.8$, CH); 2.93 (s, 6H, NMe_2); 1.46 (d, 3H, $^3J_{HH} = 6.8$, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ: 180.5 (CS); 150.3 (CN); 142.7 (Carom.); 128.5–127.4–126.0 (CHarom.) 54.0 (CH); 40.3 (NMe_2); 21.5 (CH_3). $[\alpha]_D = +179$ ($c = 4.88$, $CHCl_3$).

*4.2.2.10. (+)-N-(S)-1-phenylethyl-N′-paranitromethylphenyl-thiourea **(12)** [20]*. M.W.: 301.380. Yield: 87%, m.p.: 114–115°C. Analysis: Found (calc. for $C_{15}H_{15}N_3O_2S$) C 59.89 (59.78); H 5.11 (5.02); N 13.93 (13.94). FT-IR (KBr) (cm^{-1}): 3343–3200 (NH), 3063, 3029, 2974, 2931, 2873 (CH), 1596 (C═S), 1531, 1453, 1424, 1345, 1303, 1244, 1192, 1111, 1020, 853, 761, 747, 700. ^1H NMR ($CDCl_3$) δ: 8.75 (br s, 1H, $NHC_6H_4NO_2$); 8.1–7.2 (M, 9H, arom.); 6.98 (br s, 1H, NH); 5.58 (m, 1H, CH); 1.58 (d, 3H, $^3J_{HH} = 6.8$, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ: 178.9 (CS); 143.6–141.4 (Carom); 128.9–128.0–126.1–125.0–122.2 (CHarom.); 54.5 (CH); 21.7 (CH_3). $[\alpha]_D = +37$ ($c = 5.00$, $CHCl_3$).

4.3. Catalytic runs

The hydroformylation reactions are performed in a 25-ml stainless-steel autoclave equipped with a magnetic heating stirrer. Catalytic solution is contained in a glass vessel. Yield and selectivity are determined by GLC using *n*-decane as internal standard.

Typical run: The ligand and the rhodium(I) precursor (5.10^{-5} mol) are introduced into the autoclave, suspended in toluene (10 ml, [Rh] = 5.10^{-3} M), and styrene (2 ml, 300–350 equivalents) is then added. The autoclave is purged under vacuum/argon, and pressurized at room temperature with 20 bar of dihydrogen and 20 bar of carbon monoxide. The reaction mixture is heated to 40°C and stirred for 18 h, then cooled, degassed, filtered over celite and analyzed by GLC. Reduction by $LiAlH_4$ produced alcohols with no ee changes [31], which are used to determine enantioselectivity by HPLC over a chiral column.

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