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N,N- and N,S-ligands for the enantioselective hydrosilylation of acetophenone with iridium catalysts

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Abstract

Enantiomerically pure C_2-symmetric diamines and dithioureas as well as a series of monothioureas have been tested as chiral inducers for hydrosilylation of acetophenone with iridium catalysts. Some new N,S-ligands have been synthesized in good yields, one of them bearing four chiral centers. Enantioselectivities with dithioureas are better than the ones observed with analog diamine ligands. Up to 74% e.e. was reached for acetophenone hydrosilylation with a 10-fold excess of ligand versus iridium precursor.

Keywords: Asymmetric catalysis; Iridium(I) catalysts; Ketone hydrosilylation; Chiral diamines; Chiral dithioureas

1. Introduction

Asymmetric hydrosilylation of arylketones with transition metal catalysts containing chiral ligands is a useful synthetic route to optically active alcohols [1,2]. A large variety of chiral ligands can be used for this purpose such as oxazolines [1,3], phosphines [4], phosphinooxazolines [5], phosphites [6] and imines [1]. If phosphorus containing ligands have a high efficiency in asymmetric reduction of ketones they suffer some disadvantages such as difficult synthesis, high cost and limited stability. In the case of the hydrosilylation of ketones chiral phosphines did not achieve high enantioselectivity, however some nitrogen-containing organic ligands, as reported by Brunner's group, attained an extremely high level of enantiomeric excess (95–99% e.e.) with Pythia-[Et, H]-Rh [7] and Pybox-^{i}Pr-Rh catalysts [8]. In these species, the N and S atoms are coordinated to the Rh center.

We are interested in the use of optically pure thiourea ligands for asymmetric catalysis. Only recently, thioureas are recognized as ligands for transition metal catalysts. Few structures of such species have been reported in which the sulfur atom of the thiourea is bound to the Rh center [9]. We have focussed on a theoretical approach of the Rh–thiourea ligands and density functional theory (DFT) calculations suggested that in the more stable species the ligand is only coordinated through the sulfur atom [10a]. Experimental studies in hydrogen transfer reduction of acetophenone also indicated that thiourea behaves as an S-ligand rather than an N-ligand [10b]. Thiourea ligands, complexed to Ru, have previously afforded good enantioselectivities in hydrogen transfer reduction of ketones (94% e.e.) [11] and hydrogenation of enamides (70% e.e.) [12]. They are easy to prepare

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in good yields and very stable. In these paper, we describe the synthesis of some new thioureas, one of them bearing four chiral centers. We then report the use of diamine ligands and corresponding dithioureas as chiral inductors for the iridium catalyzed hydrosilylation of acetophenone. Various monothioureas have also been tested.

2. Asymmetric hydrosilylation of acetophenone

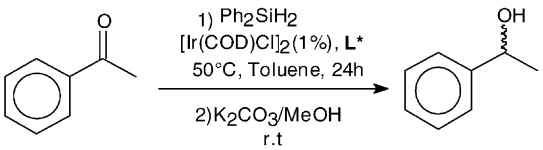
The catalysts are prepared in toluene just before their use by addition of the chiral ligand to the metal precursor. This solution is stirred at 50 °C, 10 min before adding diphenylsilane and acetophenone. The reaction led to the corresponding silyl alkyl ether. After hydrolysis both enantiomers of 1-phenylethanol are obtained (Scheme 1). The enantiomeric excesses were determined by chiral GC.

2.1. Use of diamine ligands

Enantiomerically pure C_2-symmetric diamines **1**, **2** and **3** [13] (Scheme 2), were examined as ligands in the hydrosilylation of acetophenone with $[Ir(COD)Cl]_2$ in a 100/2.5/1 (acetophenone/diamine/Ir) molar ratio, achieving 44, 98 and >99%, respectively, yield but low enantioselectivities were observed (<13%) in all cases.

2.2. Use of monothiourea ligands

Enantiomerically pure monothiourea ligands **4**, **5** [14] and **6** [15] (Scheme 2) were used in the same procedure as described for diamines. As shown in Table 1, if monothioureas **4** and **5** are not suitable for this reaction, the iridium catalyst containing C_2-symmetric ligand **6** induced good conversions and encouraging enantioselectivities. Value of e.e. increases with increasing ligand/metal ratio, as often observed in asymmetric hydrosilylation of acetophenone [1]: the use of 6 equivalents of thiourea **6** improved enantioselectivity, but only 25% e.e. was attained.



Scheme 1. Asymmetric hydrosilylation of acetophenone.

Table 1
Asymmetric hydrosilylation of acetophenone with monothiourea ligands **4**–**6**

Ligand	L*:Ir	Time (h)	Yield (%)	e.e. (%)
4	5:1	5	39	4(*R*)
5	5:1	5	33	15(*R*)
6	2.5:1	5	96	10(*S*)
6	4:1	19	97	20(*S*)
6	6:1	24	95	25(*S*)

Toluene, 50 °C, 1% catalyst.

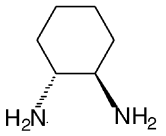
2.3. Use of dithiourea ligands

Dithiourea **7**, **8** and **9a** (Scheme 2) were obtained in good yields (>90%), as we have already described [11,13b] by reaction of the corresponding enantiomerically pure diamines with two equivalents of the desired isothiocyanate. The same procedure was used to synthesize the new N,S-ligand **9b** which is the cyclohexyl analogue of ligand **7** (Scheme 3).

Using an enantiomerically pure isothiocyanate afforded the preparation of a dithiourea containing four chiral centers. We first synthesized the (*R*)-phenylmethylisothiocyanate from the corresponding chiral amine [16] (Scheme 4). Ligand **10** was formed from reaction of the obtained chiral isothiocyanate with (*R*,*R*)-cyclohexanediamine (Scheme 3).

These dithiourea ligands were used in the reduction of acetophenone by hydrosilylation in the presence of $[Ir(COD)Cl]_2$ in a molar ratio of 100/3/1 (acetophenone/dithiourea/Ir). With dithioureas **7**, **8**, **9b**, no chiral induction was observed despite good conversions (83–93% yield). Ligand **10** was also tested in the same conditions but no enantioselectivity was detected. Even when this ligand was used with $[Rh(COD)_2]BF_4$, it led to disappointing results: 25% yield and only 30% e.e. after 24 h.

From all the tested dithioureas, only ligand **9a** led to encouraging e.e. values (Table 2). Enantioselectivity increased over the course of the reaction when the catalyst was prepared as described for diamine ligands (*method A*: $[Ir(COD)Cl]_2$ + **9a** + Ph_2SiH_2, stirred 10 min at 50 °C, +acetophenone). This suggests that the enantioselective catalyst is slowly formed during



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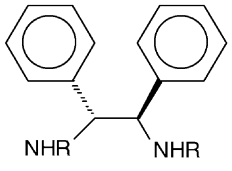
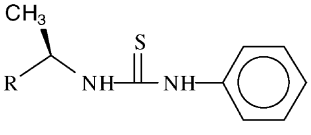
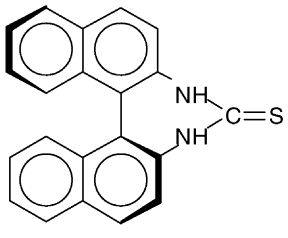


2: R=H **3:** R=CH_3



4: R=C_6H_{11} **5:** R=C_6H_5



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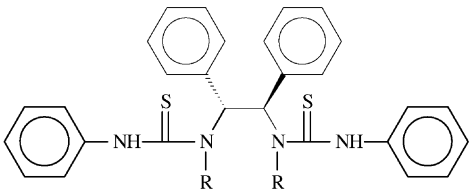
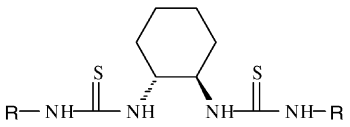
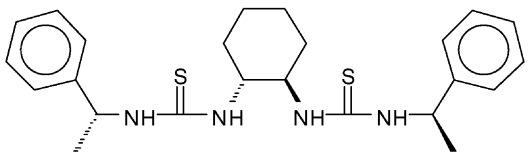


7: R=H **8:** R=CH_3

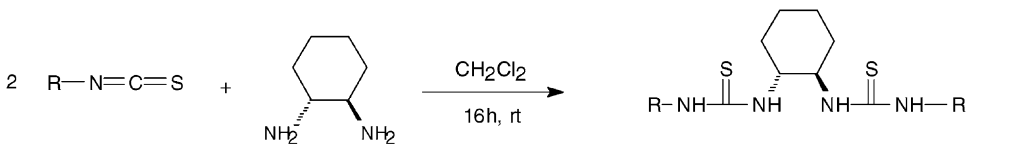


9a: R=C_6H_5 **9b:** R=C_6H_{11}



10: R=(R)-$CH(CH_3)C_6H_5$

Scheme 2. Amine and thiourea ligands for asymmetric hydrosilylation of acetophenone.

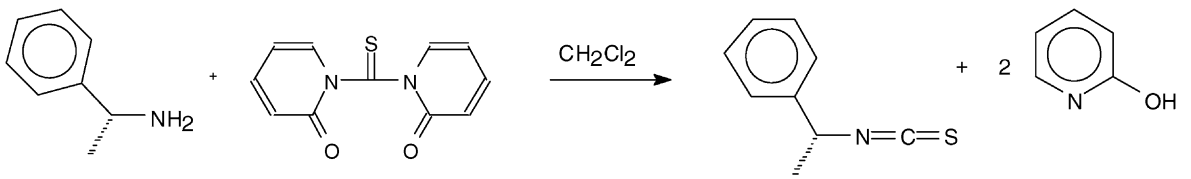


9a: R=C_6H_5

9b: R=C_6H_{11}

10: R=(R)-$CH(CH_3)C_6H_5$

Scheme 3. Synthesis of dithioureas **9** and **10**.



Scheme 4. Synthesis of 1-(*R*)-phenylethylisothiocyanate.

the reaction in the presence of a slight excess of diphenylsilane. After various essays of catalyst preparation we noticed that when acetophenone was added 5 h after the silane (*method B*: $[Ir(COD)Cl]_2$ + **9a** + Ph_2SiH_2, stirred 5 h at 50 °C, +acetophenone) higher e.e. was observed and this value (~52%) does not change significantly when increasing the reaction time. Therefore, diphenylsilane plays a particular role in the formation of the enantioselective species from $[Ir(COD)Cl]_2$ and ligand **9a**.

A recent kinetic study [17] demonstrated that the order of addition of the reactants influences the hydrosilylation reaction rate: when acetophenone was added before the silane to the Rh/BINAP catalyst, an inactive complex was formed (saturation effect) and then the hydrosilylation rate decreased. Thus, the turnover limiting step is more likely the oxidative addition of silane. In our case, this step is probably slow, which explains the e.e. increase when the silane/ligand/iridium mixture was stirred 5 h instead of 10 min before adding acetophenone.

Table 2
Asymmetric hydrosilylation of acetophenone with ligand **9a**: influence of the catalyst preparation

Catalyst preparation	Reaction time (h)	Yield (%)	e.e. (*R*) (%)
$[Ir(COD)Cl]_2$ + **9a**	0.67	43	18
Method A	6	96	35
$[Ir(COD)Cl]_2$ + **9a**	1	10	51
Method B[a]	6	23	52
	24	58	54
$[Ir(COD)_2]BF_4$ + **9a**	6	9	58
Method B[b]	24	26	57

Toluene, 50 °C, 1% catalyst, L*:Ir = 3:1.
[a] *Method A*: $[Ir(COD)Cl]_2$ + **9a** + Ph_2SiH_2, stirred 10 min at 50 °C, +acetophenone.
[b] *Method B*: $[Ir(COD)Cl]_2$ + **9a** + Ph_2SiH_2, stirred 5 h at 50 °C, +acetophenone.

Brunner [1] reported that in several cases, an excess of imine or Pythia chiral ligand is needed in order to improve the enantioselectivity of rhodium catalyzed ketone hydrosilylations. We thus studied the influence of the amount of ligand on the iridium/dithiourea **9a** catalyzed acetophenone hydrosilylation
(Fig. 1).

We likewise noticed an e.e. increase but the catalytic activity decreased significantly: 74% e.e. was reached and only 30% conversion with a 10-fold excess of **9a** versus iridium. This trend suggests that various species are formed when iridium is mixed with the dithiourea ligand and diphenylsilane and that among those complexes at least one is an enantioselective catalyst. In our hydrosilylation conditions, the iridium precursor itself is an active catalyst (100% yield in 1 h) and if some of it is left uncoordinated to the dithiourea ligand, acetophenone conversion is favored without enantioselection.

In a recent theoretical study concerning rhodium/thioureas complexes, we pointed out that the main coordination mode of dithioureas is η^1 and takes place through the lone pair on S atoms [18]. Thus, we can assume that in the iridium/dithiourea **9a** species, the ligand is bounded through the two sulphur atoms. In our hydrosilylation conditions, various complexes containing ligand **9a** can be formed, such as **II**, **III** and **IV** as shown in Fig. 2. Considering this chemical equilibrium we notice that large amounts of dithiourea **9a** help the formation of complexes **II**, **III** and **IV**. From those species, unsaturated complex **II** is likely the enantioselective catalyst for the hydrosilylation reaction. This is in accordance with the experimental enantioselectivity improvement observed when increasing **9a**/Ir ratio (Fig. 1). At the same time, conversion diminishes, which can be explained by the complexation of a second dithiourea giving coordinatively saturated species **IV** On the other hand, the high conversions observed

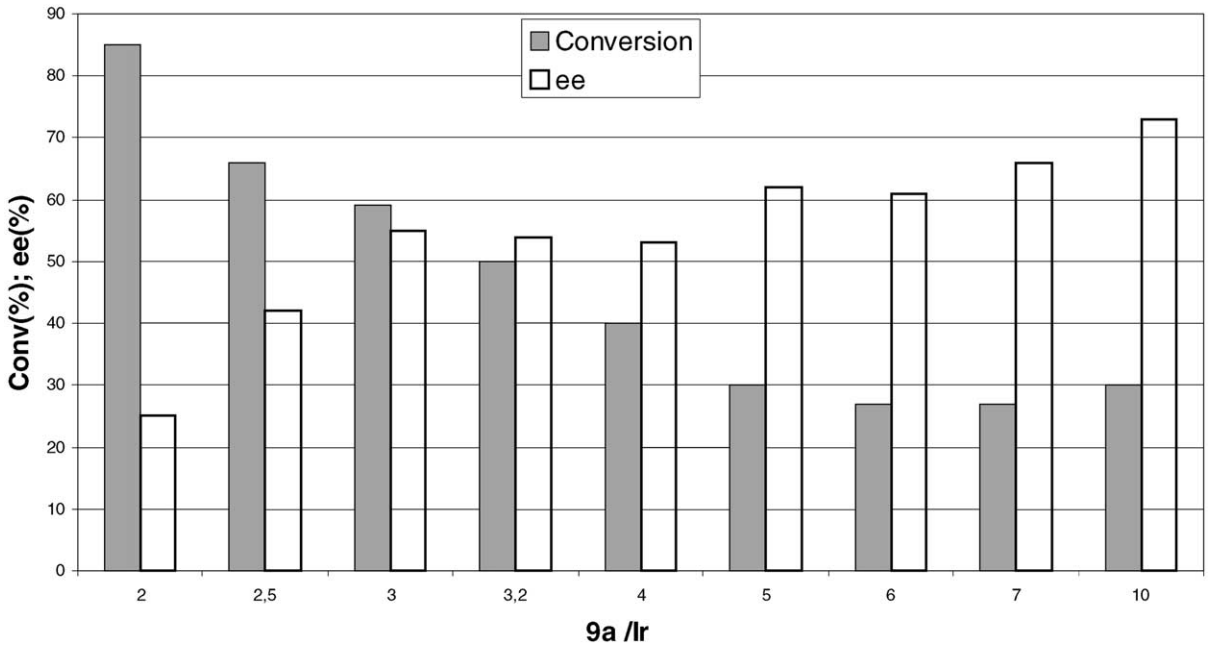
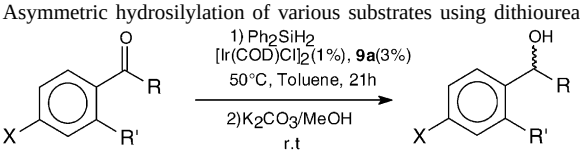


Fig. 1. Influence of ligand **9a** vs. $[Ir(COD)Cl]_2$ molar ratio on the asymmetric hydrosilylation of acetophenone (toluene, 50 °C, 1% catalyst, 24 h).

$$[Ir(COD)Cl]_2 + H_2SiPh_2 + \mathbf{9a} \rightleftharpoons \begin{cases} Ir(HSiPh_2)H(COD)Cl & \text{complex } \mathbf{I} \\ Ir(HSiPh_2)H(\mathbf{9a})Cl & \text{complex } \mathbf{II} \\ Ir(\mathbf{9a})(COD)Cl & \text{complex } \mathbf{III} \\ Ir(\mathbf{9a})_2Cl & \text{complex } \mathbf{IV} \\ \ldots\ldots\ldots & \end{cases}$$

Fig. 2. Some of the species potentially formed during the catalyst preparation.

Table 3
Asymmetric hydrosilylation of various substrates using dithiourea **9a**



R	R′	X	Yield (%)	e.e. (*R*) (%)
CH_3	H	H	50	55
CH_3	H	CF_3	24	13
CO_2CH_3	H	H	53	0
$(CH_2)_2CH_3$	H	H	23	9
$CH(CH_3)_2$	H	H	6	12
$C(CH_3)_3$	H	H	2	0
$-(CH_2)_3-$		H	34	28

for small ligand/Ir ratios are mostly due to the presence of achiral complex **I** and remaining $[Ir(COD)Cl]_2$.

We extended our study to various acetophenone derivatives. Their hydrosylilation was carried out with the dithiourea **9a**/Ir system (catalyst preparation according to *method B*). Low conversions and enantioselectivities were obtained for all the substrates used (Table 3).

The bulky R groups seem to hamper the ketone approach to the iridium center, which has a negative effect on reaction yields. When CF_3 is anchored to the aromatic ring, unsatisfactory results are observed, maybe to the decrease of the electron density of the C=O bond, thus weakening its interaction with the iridium atom of the complex.

3. Conclusion

Asymmetric hydrosilylation of acetophenone was carried out with iridium catalysts containing chiral diamines or thiourea ligands. Dithioureas are better asymmetric inducers than the corresponding diamines. Indeed, we have proved that C_2-symmetric dithioureas could act as a new type of ligands for asymmetric hydrosilylation of ketones. Thus, dithiourea **9a** induced encouraging enantioselectivities and 74% e.e. was attained with a 10-fold excess versus iridium. As conversion stayed low due to the presence of various complexes in the reaction mixture, we are now focusing on the preparation and separation of the iridium–dithiourea **9a** enantioselective species. Although the obtained enantioselectivity is modest compared to those of Pythia containing catalysts, dithiourea use in asymmetric catalysis is obviously at a very early stage and we thus continue studying such N,S-ligands.

4. Experimental

4.1. General

All the organic and organometallic reagents used were pure commercial products. The solvents are reagent grade. All manipulations of iridium compounds are carried out under an argon atmosphere. Enantiomerically pure diamines (1*R*,2*R*)-cyclohexanediamine **1** and (1*R*,2*R*)-(+)-*N*,*N*′-1,2-diphenylethylenediamine **2** were obtained from Aldrich, isothiocyanate from Fluka. (1*R*,2*R*)-(+)-*N*,*N*′-dimethyl-1,2-diphenylethylenediamine **3** was synthesized according to recently published procedures [13a,19]. The corresponding dithiourea compounds **7**, **8** and **9a** were prepared and characterized as already described [11,13b] as well as the preparation and characterization of monothioureas **4**, **5** [14], **6** [15] and (*R*)-phenylmethylisothiocyanate [16].

Melting points (mp), noncorrected, were determined with an Electrothermal 9100 apparatus. Elemental analysis (C, H, N, S) were obtained from the Service Central d'Analyse of the CNRS (Solaize). High resolution mass spectra (HRMS) were carried out on a Finnigan MAT 95xL by the UCBL Centre de Spectroscopie de Masse. The e.e. values and yields were determined by analytical GLC with a chiral Lipodex A (25 m) or a Cyclodex β (30 m) column on Shimadzu GC-14A chromatograph using a flame-ionization detector and Shimadzu C-R6A integrator. IR spectra (KBr plates) were recorded on a FT Bruker Vektor 22 spectrometer. $[\alpha]_D$ were determined with a Perkin-Elmer 241 polarimeter (l = 1 dm; 25 °C; concentration c in g/ml). ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 FT spectrometer, (200.13 MHz for ^1H and 50.32 MHz for ^{13}C) δ values are given in ppm.

4.2. General synthesis of dithioureas

To a solution of the diamine (1 mmol) in 5 ml of dichloromethane isothiocyanate (2 mmol) was added. The solution was stirred overnight at room temperature. The ligand was precipitated in pentane, filtered through a Millipore filter (pore size 0.10 μm) and washed with pentane. Finally, it was dried in vacuo.

4.3. Synthesis of (R,R)-1,2-diaminocyclohexyl-dicyclohexyldithiourea (*9b*)

Product **10** was synthesized according to the general procedure given for dithioureas. Isolated yield: 84%; mp = 230 °C. $[\alpha]_D$ = +90.2 (c = 0.01, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ ppm = 1.1–2.5 (18H, m), 3.8 (2H, m), 4.3 (2H,m), 6.2 (2H, m, NH), 7.1 (2H, m, NH). ^{13}C NMR ($CDCl_3$): δ = 179.7 (C=S), 52.5 (CH), 33 (CH_2), 32.8 (CH_2), 32.4 (CH_2), 25.4

(CH_2), 24.7 (CH_2). IR (KBr), $\nu(cm^{-1})$ = 1558(NH) and 1082(C=S). MSHR calculated for $C_{20}H_{36}N_4S_2$ H^+ = 397.24596; found = 397.24498 Anal. Calcd. (%) for $C_{20}H_{36}N_4S_2$: C, 60.56%; H, 9.15%; N, 14.12%; S,16.17%. Found: C, 60.24%; H, 9.36%; N, 14.06%; S, 16.17%.

*4.4. Synthesis of (R,R)-1,2-diaminocyclohexyl-di[-(R)-phenylethyl]dithiourea (**10**)*

Product **11** was synthesized according to the general procedure given for dithiouras. Isolated yield: 85%; mp = 137 °C. $[\alpha]_D$ = −90.8 (c = 0.01, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ ppm = 1.2–2.2 (8H, m), 1.5 (6H, d, J=), 4.1 (2H, m), 5.2 (m, 2H, NH), 6.6 (m, 2H, NH), 7.4 (m, 10H). ^{13}C NMR ($CDCl_3$): δ = 180.3 (C=S), 142.2, 129, 127.7, 126 (C_6H_5), 53.9 (CH), 31 (CH_2), 25 (CH_3), 22.5 (CH_2). IR (KBr), $\nu(cm^{-1})$ = 1543(NH) and 1083(C=S). MSHR calculated for $C_{24}H_{32}N_4S_2$ H^+ = 441.21466; found = 441.21464. Anal. Calcd. (%) for $C_{24}H_{32}N_4S_2$: C, 65.42%; H, 7.32%; N, 12.71%; S, 14.55%. Found: C, 65.71%; H, 7.36%; N, 12.81%; S, 14.32%.

4.5. Typical procedure for catalytic hydrosilylation test

In a 5 ml reaction vial, under an argon atmosphere, diphenylsilane (4.29 mmol) was added to a solution of the metallic precursor (8.9×10^{-3} mmol) and desired ligand amount in 2 ml of toluene. The resulting solution was stirred 5 h at 50 °C. The substrate (2.86 mmol) was added and stirring was continued for 6–24 h at 50 °C. An aliquot of 1 ml was removed and treated with a small quantity of K_2CO_3 in 1 ml of MeOH. This mixture was stirred for 30 min at room temperature. 1 ml of H_2O was added to the mixture, the organic layer was extracted and washed with 2× 1 ml of H_2O, dried over anydrous Na_2SO_4 and filtered through Celite, before chiral CPV analysis.

Acknowledgements

We thank Geneviève Heraud for valuable advice concerning chiral GPC.

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