Aminosulf(ox)ides as Ligands for Iridium(I)-Catalyzed Asymmetric Transfer Hydrogenation

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A new class of efficient catalysts was developed for the asymmetric transfer hydrogenation of unsymmetrical ketones. A series of chiral *N,S*-chelates (**6**−**22**) was synthesized to serve as ligands in the iridium(I)-catalyzed reduction of ketones. Both formic acid and 2-propanol proved to be suitable as hydrogen donors. Sulfoxidation of an (*R*)-cysteine-based aminosulfide provided a diastereomeric ligand family containing a chiral sulfur atom. The two chiral centers of these ligands showed a clear effect of chiral cooperativity. In addition, aminosulfides containing two asymmetric carbon atoms in the backbone were synthesized. Both the sulfoxide-containing *β*-amino alcohols and the aminosulfides derived from 1,2-disubstituted amino alcohols gave rise to high reaction rates and moderate to excellent enantioselectivities in the reduction of various ketones. The enantioselective outcome of the reaction was favorably affected by selecting the most appropriate hydrogen donor. Enantioselectivities of up to 97% were reached in the reduction of aryl-alkyl ketones.

Introduction

The enantioselective synthesis of optically active secondary alcohols, which form an important class of intermediates for fine chemicals and pharmaceuticals, has been studied extensively. One of the most attractive methods for synthesizing chiral alcohols is asymmetric transfer hydrogenation of prochiral ketones. The product alcohols are obtained in high yields and good enantiomeric excesses, and the fractional yields of side products are low. Furthermore, the reaction conditions are relatively mild and do not require the use of molecular hydrogen, because the organic solvent, often 2-propanol, can serve as a hydrogen donor. Nitrogen-based ligands are often the ligands of choice in systems developed so far, inducing high enantiomeric excesses in combination with high catalytic activities.

An inherent problem of this potentially useful asymmetric catalytic reaction is the reversibility of the process, because of the similarities between 2-propanol and the product alcohol. Even if the reaction proceeds with excellent kinetic enantiofacial differentiation, the equilibration frequently causes a decrease in the enantiomeric purity of the alcoholic products. Also, the lack of a thermodynamic driving force prevents complete conversion. To minimize the unfavorable reaction in 2-propanol, catalysis must be performed using substrate concentrations as low as 0.1 M.[1]

An attractive alternative for 2-propanol as a hydrogen donor is formic acid. The use of the latter results in irreversible reactions due to CO_2 evolution, thus preventing racemization. As a result of this irreversibility, reactions can be carried out at higher substrate concentrations (i.e., >1 M) and higher temperatures without the disadvantage of decreasing enantiomeric excess. Formic acid proved to be a very useful hydrogen donor in ruthenium(II)-catalyzed transfer hydrogenation using TsDPEN as the ligand, which was developed by Noyori and co-workers [TsDPEN = *N*-(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine].[2] Catalyst stability is an important issue when using the azeotropic mixture of formic acid/triethylamine as a hydrogen donor. Only a few catalysts gave rise to high activities when formic acid was used as a hydrogen donor in hydrogen transfer reactions. Most catalysts used so far are only stable in 2-propanol.

One of the first successful classes of transfer hydrogenation catalysts that induced high enantioselectivities was developed by Pfaltz and co-workers in 1991.[3] These catalysts contained C_2-symmetric bioxazole ligands that displayed good activity in iridium(I)-catalyzed hydrogen transfer reactions. Aryl-alkyl ketones were readily reduced providing the corresponding alcohols in 47−91% enantiomeric excess. Also Noyori's diamine ligand (i.e., TsDPEN) was used in iridium(I)-catalyzed hydrogen transfer reactions in 2-propanol, resulting in an enantioselectivity of 92% in the reduction of acetophenone.[4] *N*-Acetyl-(*S*)-methionine-(*R,S*)-sulfoxide (AMSO) gave rise to enantioselectivities of up to 71% in rhodium-catalyzed enantioselective transfer hydrogenation in 2-propanol.[5]

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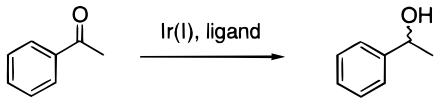
Scheme 1. Asymmetric Transfer Hydrogenation of Acetophenone



To the best of our knowledge, the use of formic acid as a hydrogen donor has never been investigated in iridium(I)-catalyzed asymmetric hydrogen transfer reactions. In this paper, the development of new catalysts that are stable in formic acid/triethylamine is described. The resulting systems are among the most active catalytic systems found so far for asymmetric hydrogen transfer reactions based on iridium(I) complexes with simple aminosulf(ox)ides as ligands.

N,*S*-Chelates have been widely used in asymmetric catalysis.[6−15] They create additional possibilities compared to *N*,*N*- and *N*,*O*-chelates, because the sulfur atom becomes chiral when coordinated to the metal.[16−21] A new class of ligands is formed by oxidation of the sulfur atom. Here, the sulfur atom itself is chiral and possesses different electronic and polarity characteristics.

Two series of *N*,*S*-chelates were synthesized and optimized in terms of activity and selectivity toward the reduction of acetophenone by variations in ligand substitution. The influences of the catalyst precursor, the ligand stoichiometry, the reaction temperature, and the substrate concentration were studied. Both formic acid and 2-propanol proved to be useful as hydrogen donors. The enantioselective outcome of the reaction was optimized by selecting the most appropriate hydrogen donor.

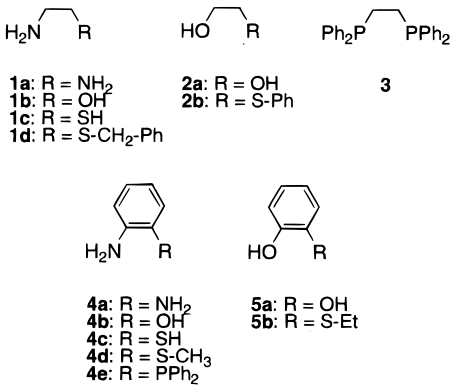
Results and Discussion

Two different series of achiral nitrogen-containing ligands (**1**−**5**) were tested in the iridium(I)-catalyzed transfer hydrogenation of acetophenone using formic acid as a hydrogen donor (Scheme 1).

Table 1. Hydrogen Transfer Reduction of Acetophenone Using Ligands 1−5[a]

entry	ligand	R	conv. (1 h) (%)[b]	$TOF_{initial}$ (mol mol^{-1} h^{-1})[c]
1	**1a**	NH_2	60	50
2	**1b**	OH	0.5	5
3	**1c**	SH	0.5	6
4	**1d**	S−CH_2−Ph	>99	250
5	**2a**	OH	0.4	4
6	**2b**	S−Ph	0.3	7
7	**3**	−	0.1	2
8	**4a**	NH_2	20	70
9	**4b**	OH	2	20
10	**4c**	SH	6	10
11	**4d**	S−CH_3	10	40
12	**5a**	OH	0.5	−
13	**5b**	S−CH_2−CH_3	<0.1	−
14	**1d**	S−CH_2−Ph	58[d]	700[d]

[a] The reaction was performed at 60 °C using 4 mmol of substrate in 3 mL of a formic acid/triethylamine (5:2) solution. Substrate:$[IrCl(COD)]_2$:ligand = 400:1:5. [b] Conversions were determined by GLC analysis. [c] Initial turnover frequencies were measured after 5 min of reaction time. [d] Substrate:$[IrCl(COD)]_2$:ligand = 1000:1:5.



A standard set of conditions was used, consisting of 0.5 mol % $[IrCl(COD)]_2$ as the catalyst precursor, 2.5 mol % ligand in a 5:2 azeotropic mixture of formic acid/triethylamine at 60 °C. Conversions were monitored during the reaction. Table 1 shows that the use of aminosulfide **1d** (R = S−CH_2−Ph, entries 4 and 14, Table 1) resulted in the formation of the most active catalyst. The use of diamine-type ligands in iridium(I)-catalyzed transfer hydrogenation (entries 1 and 8, Table 1) gave rise to lower activities under these conditions. Introduction of various substituents (R_1 and R_2) in the carbon backbone of **1d** provides optically active aminosulfides, fitting the general structure depicted in Figure 1.

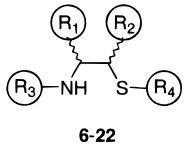


Figure 1. Ligands **6**−**22**.

Optimization in terms of activity and selectivity toward the transfer hydrogenation of acetophenone was carried out using a variety of *N*,*S*-chelates containing different R_1−R_4 substituents. Conversions and enantioselectivities were monitored during the reaction. The enantioselectivity proved to be constant in time for all catalytic reactions described, unless stated otherwise.

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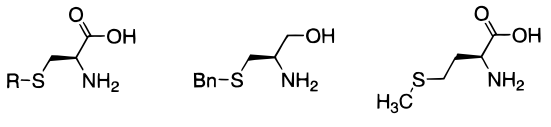
Table 2. Hydrogen Transfer Reduction of Acetophenone Using Ligands 6−12[a]

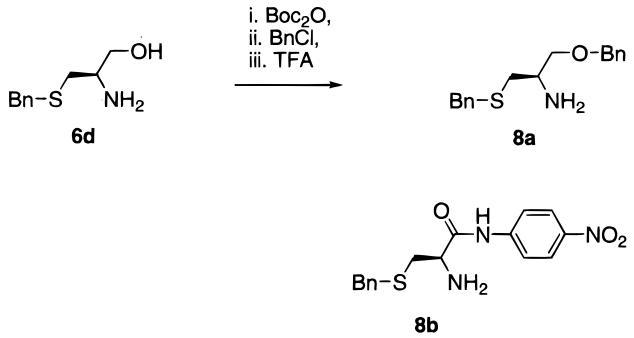
entry	ligand	time (h)	conv. (%)[b]	ee (%)[c]	confign
1	**6a**	20	96	10	*S*
2	**6b**	1	26	12	*S*
3	**6c**	66	94	10	*S*
4	**6d**	1	98	12	*S*
5	**6e**	20	75	10	*S*
6	**7**	20	24	9	*S*
7	**8a**	1	97	14	*S*
8	**8b**	1	58	18	*S*
9	**9**	1	97	5	*S*
10	**10**	20	97	7	*S*
11	**11a**	40	20	18	*S*
12	**11b**	40	<1	nd[d]	−
13	**12**	1	56	35	*S*
14	**12a**	1	56	27	*R*
15	**12b**	0.5	99	65	*S*

[a] The reaction was performed at 60 °C using 4 mmol of substrate in 3 mL of a formic acid/triethylamine (5/2) solution. Substrate: $[IrCl(COD)]_2$:ligand = 400:1:5. [b] Conversions were determined by GLC analysis. [c] Determined by capillary GLC analysis using a chiral cycloSil-B column. [d] nd = not determined.

***N,S*-Chelates Based on (*R*)-Cysteine.** The introduction of a variety of R_1 substituents could easily be achieved in sulfur-containing amino acids. A number of L-cysteine and L-methionine derivatives were synthesized and applied in the iridium(I)-catalyzed reduction of acetophenone. Optically pure *S*-methylcysteine (**6a**) and methionine (**7**) were used to study the effect of the ligand bite angle. Table 2 shows that the two-carbon-bridged ligand **6a** displayed much higher activities than the three-carbon-bridged methionine ligand **7**, while the selectivities were similar (entries 1 and 6, Table 2).

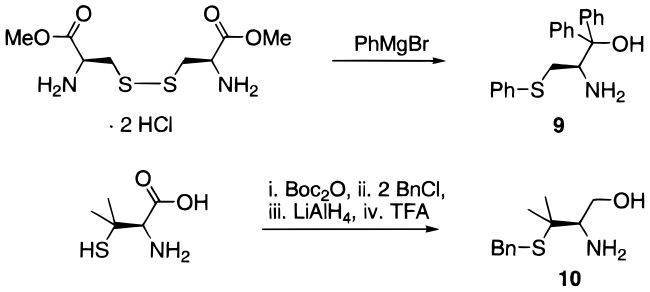


Scheme 2. Ligands 8a and 8b



To investigate the difference in reactivity of amino acids versus amino alcohols, **6b** was compared with **6d**. Reduction of the amino acid **6b** to the amino alcohol **6d** provided a second major increase of the reaction rate without a change in enantioselectivities (entries 2 and 4, Table 2). To optimize enantioselectivities for this system, the substituents R_1−R_4 were systematically varied. Starting from the commercially available *S*-benzyl-(*R*)-cysteinol (**6d**), the hydroxyl group in the R_1 substituent was functionalized with a benzyl group, and after deprotection of the amine functionality, the oxygen-substituted aminosulfide **8a** was obtained (Scheme 2). The use of R_1-substituted aminosulfides **8a** and **8b** in the iridium(I)-catalyzed reduction of acetophenone did not significantly affect the activity and selectivity of the catalyst (entries 7 and 8, Table 2).

Scheme 3. Synthesis of Ligands 9 and 10



Sterically demanding R_1 substituents in amino acid derivatives were found to be very useful in asymmetric borane reductions and enantiocontrolled catalytic addition of diethylzinc to benzaldehyde, resulting in high enantioselectivities.[18,22,23] Compound **9** was obtained from (*R*)-cystine methyl ester hydrochloride by reaction with phenylmagnesium bromide (Scheme 3).[22] The substituted aminosulfide **9**, however, did not induce higher enantioselectivities compared to the unsubstituted **6d** (entry 9, Table 2).

R_2-disubstitution was introduced to create more steric bulk in the carbon backbone. Starting from (*R*)-penicillamine, aminosulfide **10**, containing two methyl substituents on the α carbon atom, was synthesized (Scheme 3). However, the use of the substituted aminosulfide **10** did not induce higher enantioselectivities compared to the unsubstituted **6d** (entry 10, Table 2).

It has been reported that the catalyst activity or selectivity is most strongly affected by substituents that are in close proximity to the coordinating atoms.[24] For the sulfur-containing amino acid derivatives we describe here, we assume a bidentate *N*,*S*-coordination fashion. This assumption is supported by the results from Table 1, which show that ethanolamine, representative for *N*,*O*-coordination, does not catalyze the reduction of acetophenone under the applied reaction conditions. Also, varying the R_1 and R_2 substituents in **6d** did not change the enantioselective outcome of the reaction. Variations in the R_3 and R_4 substituents on the nitrogen and sulfur atoms are expected to give rise to larger effects on the enantioselectivity, as they are positioned closer to the catalytic center than the oxygen atom. Bulky R_3 substituents were introduced by substitution of the primary amine functionality in **6d** by a tosyl (**11a**) and a *tert*-butoxycarbonyl group (**11b**) (Scheme 4). The use of N-substituted *N*,*S*-chelates in the iridium(I)-catalyzed transfer hydrogenation of acetophenone resulted in a considerable loss of catalytic activity, while the enantioselectivity was hardly affected (entries 11 and 12, Table 2). Because the introduction of a substituted amide not only increases steric hindrance but also reduces the donating capacity of the nitrogen atom, the cause of the catalyst deactivation remains unresolved.

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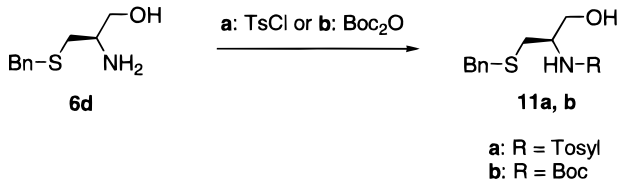
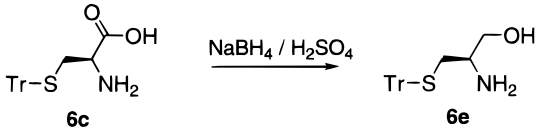
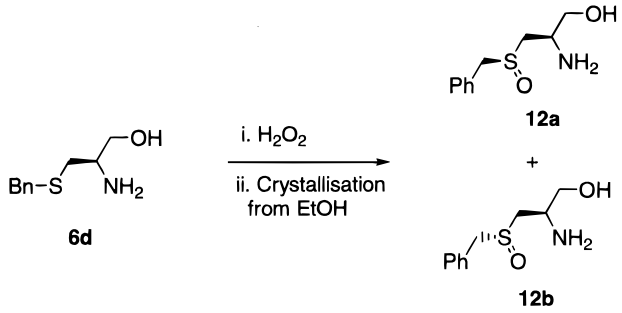
Scheme 4. Synthesis of Ligands 11a and 11b



Scheme 5. Synthesis of Ligand 6e



Scheme 6. Synthesis of Ligand 12[a]



[a] Diastereomers **12a** and **12b** were separated by repeated crystallization from ethanol.

An *N*,*S*-chelate containing a bulky R_4 substituent on the sulfur atom was synthesized by reduction of *S*-trityl-(*R*)-cysteine (**6c**) to *S*-trityl-(*R*)-cysteinol (**6e**) (Scheme 5). Standard $LiAlH_4$ reduction failed in the case of these sulfur-containing amino acids. A milder method, developed by Abiko et al. for large-scale reductions of amino acids using sodium borohydride and sulfuric acid, provided the desired product (**6e**).[25] Replacement of the benzyl group by a trityl group resulted in a dramatic decrease in activity, while the selectivity was identical in both cases (entries 3 and 5, Table 2).

An additional possibility for creating a more sterically hindered environment around the sulfur moiety is oxidation of the sulfur atom, which provides a different class of ligands. The presence of a sulfoxide moiety also changes the electronic properties of the ligand. Moreover, sulfoxidation results not only in an extra substituent on the sulfur atom but also in an additional chiral center in the ligand. A 1:1 mixture of two diastereomers of *S*-benzyl-(*R*)-cysteinol sulfoxide (**12a** and **12b**) was formed using hydrogen peroxide as the oxidant (Scheme 6). All attempts to achieve asymmetric sulfoxidation, using either chiral titanium catalysts[26−29] or chloroauric acid,[30] failed. The polar sulfoxide products could not be separated from the reaction mixture by extraction or chromatographic methods. We succeeded, however, in separating the two diastereomers by repeated crystallization from either ethanol or 2-propanol. The configuration of diastereomer **12a** [i.e., *S*-benzyl-(*R*)-cysteinol (*S*)-sulfoxide] was determined by X-ray analysis.

When the 1:1 diastereomeric mixture of **12a** and **12b** was used in catalysis, the enantiomeric excess increased to 35% from 12% for **6d**. At the same time, the catalyst activity decreased by a factor of 2 (entry 13, Table 2). Interestingly, a marked difference in stereoselection was found when the two diastereomers were used separately. The diastereomer of *S*-benzyl-(*R*)-cysteinol (*S*)-sulfoxide (**12a**) in combination with $[IrCl(COD)]_2$ created the opposite product configuration (i.e., *R*) compared to the diastereomeric 1:1 mixture (giving the *S* product) and had a similar reaction rate (entry 14, Table 2). The use of the diastereomer of *S*-benzyl-(*R*)-cysteinol (*R*)-sulfoxide **12b** induced an increase in enantioselectivity of up to 65%, giving the *S* product. At the same time, the reaction rate was similar to that of **6d**, resulting in >99% conversion after 1 h (entry 15, Table 2). Thus, a clear effect of chiral cooperativity was observed between the sulfoxide functionality and the α position of the amino alcohol. In addition, the use of the diastereomeric mixture of ligands nicely shows that the asymmetric transfer hydrogenation reaction is kinetically controlled, resulting in the *S* product.

***N*,*S*-Chelates Derived from (Nor)ephedrine and 2-Aminodiphenylethanol.** Introduction of two chiral centers in the carbon backbone using different R_1 and R_2 substituents was achieved starting from (1*R*,2*S*)-(nor)-ephedrine and (1*R*,2*S*)-2-aminodiphenylethanol. Ephedrine-based *β*-aminothiols and -disulfides catalyze the 1,2 addition of diethylzinc to aromatic aldehydes, producing the corresponding alcohols in high enantiomeric excess and yield.[31−33] Dieter and co-workers[34] showed that optically pure aminosulfides containing a tertiary amine functionality could easily be obtained from N-substituted ephedrine derivatives. For the synthesis of aminosulfides containing a secondary amine, a different method was used by Kellogg and co-workers.[35] Scheme 7 shows that *N*,*S*-chelates containing a primary amine functionality could be obtained starting from norephedrine and 2-aminodiphenylethanol using the latter synthetic strategy.

Starting from (1*R*,2*S*)-norephedrine, aziridine **13** was synthesized using Mitsunobu conditions. Stereoselective ring opening of the aziridine with several thiol nucleophiles provided the aminosulfides **16**−**18**, in which R_1 = methyl. Similarly, aminosulfides **19** and **20**, with R_1 = phenyl, were synthesized from aziridine **14**, which was obtained from (1*R*,2*S*)-2-aminodiphenylethanol. The R_4 substituent at the sulfur atom was varied using different sulfur nucleophiles. The results of the use of these ligands in iridium(I)-catalyzed transfer hydrogenation of acetophenone using formic acid as a hydrogen donor are summarized in Table 3.

Table 3 shows that the variation of both the R_1 substituent and the R_4 substituent largely affects the outcome of the reaction. Both the activity and the

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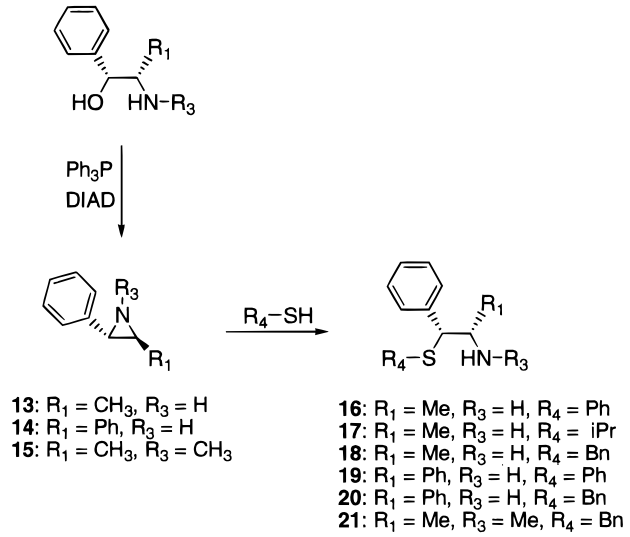
Scheme 7. Synthesis of Ligands 16−21



13: $R_1 = CH_3$, $R_3 = H$
14: $R_1 = Ph$, $R_3 = H$
15: $R_1 = CH_3$, $R_3 = CH_3$

16: $R_1 = Me$, $R_3 = H$, $R_4 = Ph$
17: $R_1 = Me$, $R_3 = H$, $R_4 = iPr$
18: $R_1 = Me$, $R_3 = H$, $R_4 = Bn$
19: $R_1 = Ph$, $R_3 = H$, $R_4 = Ph$
20: $R_1 = Ph$, $R_3 = H$, $R_4 = Bn$
21: $R_1 = Me$, $R_3 = Me$, $R_4 = Bn$

Table 3. Hydrogen Transfer Reduction of Acetophenone Using Ligands 16−22b[a]

entry	ligand	time (h)	conv. (%)[b]	ee (%)[c]	confign
1	**16**	3	52	23	*S*
2	**17**	3	>99	41	*S*
3	**18**	3	>99	65	*S*
4	**19**	3	20	42	*R*
5	**20**	18	2	58	*S*
6	**21**	5	91	42	*S*
7	**22a**	6	32	32	*S*
8	**22b**	6	9	2	*S*

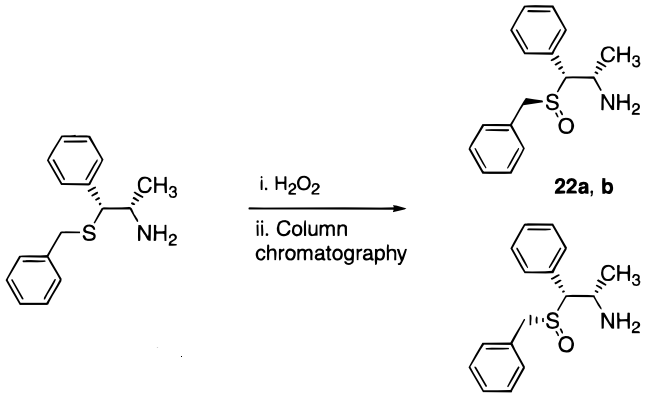
[a] The reaction was performed at 60 °C using 4 mmol of substrate in 3 mL of a formic acid/triethylamine (5:2) solution. Substrate: $[IrCl(COD)]_2$:ligand = 400:1:5. [b] Conversions were determined by GLC analysis. [c] Determined by capillary GLC analysis using a chiral cycloSil-B column.

enantioselectivity increased on changing the R_4 substituents from phenyl (**16**) to isopropyl (**17**) and to benzyl (**18**). Introduction of bulky phenyl groups at both positions R_1 and R_4 (**19**) resulted in a change of product configuration from *S* to *R*. The presence of three phenyl groups in close proximity to the metal center probably results in a change in conformation of the complex. Also, interaction between an aromatic substituent and the phenyl ring of the substrate could play a role. When the steric strain is released slightly by changing R_4 to benzyl (**20**), the product configuration changes back to *S*. To improve the enantioselectivities even further in this series of ligands, the nitrogen atom was functionalized. Starting from (1*R*,2*S*)-ephedrine, ligand **21**, which contains a methyl substituent on the nitrogen atom, was obtained (see Scheme 7).[31] As shown in Table 3, introduction of the methyl substituent at the R_3 position in **21** induced a decrease in both reaction rate and asymmetric induction (entry 6). In analogy to **12a**,**b**, the sulfide functionality in **18** was oxidized to form **22a**,**b** (Scheme 8). The diastereomers were separated by column chromatography.

As observed for **12a**,**b**, the two diastereomers **22a**,**b** showed a large difference in reaction rate and enantioselectivity. Oxidation of the sulfur atom as in **22a**,**b**, however, did not provide any further improvement in the iridium(I)-catalyzed transfer hydrogenation of acetophenone (entries 7 and 8, Table 3).

Catalyst Optimization. In the following, we describe our attempts to further optimize the iridium(I) amino-

Scheme 8. Synthesis of Ligand 22[a]



[a] Diastereomers **22a** and **22b** were separated by column chromatography.

Table 4. Hydrogen Transfer Reduction of Acetophenone Using Various Iridium Precursors[a]

entry	ligand	Ir precursor	conv. (1 h) (%)[b]	ee (%)[c]	confign
1	**6d**	$[IrCl(COD)]_2$	98	12	*S*
2	**6d**	$[Ir(COD)]BF_4$	98	12	*S*
3	**6d**	$[IrCl(COE)_2]_2$	8	16	*S*
4	**6d**	$[IrCl(1,5\text{-diMe-COD})]_2$	56	15	*S*
5	**6d**	$[IrCl(CO)_3]_n$	18	15	*S*
6	**6d**	$[IrCl_2(Cp)^*]_2$	<1	nd[d]	−

[a] The reaction was performed at 60 °C using 4 mmol of substrate in 3 mL of a formic acid/triethylamine (5/2) solution. Substrate: $[IrCl(COD)]_2$:ligand = 400:1:5. [b] Conversions were determined by GLC analysis. [c] Determined by capillary GLC analysis using a chiral cycloSil-B column. [d] nd = not determined.

sulf(ox)ide catalysts in terms of activity and selectivity by varying the catalyst precursor, the ligand stoichiometry, the reaction temperature, and the hydrogen source.

Influence of the Catalyst Precursor. The influence of the nature of the catalyst precursor on the reaction rate and enantioselectivity of this reaction was studied. Different anions, different dienes, and an iridium carbonyl precursor were used. Table 4 shows that changing the anion from Cl^- to BF_4^- does not affect the catalytic reaction. The presence of a diene in the active catalyst in rhodium-catalyzed transfer hydrogenation using 2-propanol as a hydrogen source was proved by Lemaire and co-workers.[36] Table 4 shows that the presence of a diene is also important for obtaining high reaction rates in iridium(I)-catalyzed hydrogen transfer reactions using formic acid as the H-donor (entries 1 and 3). The use of various catalyst precursors only marginally affected the stereoselective outcome of the reaction. The catalyst activity did not improve using different iridium precursors compared to $[IrCl(COD)]_2$.

Influence of the Ligand Stoichiometry. In rhodium(I)- and iridium(I)-catalyzed transfer hydrogenation, 2 equiv of ligand per metal atom is typically used. In a mechanistic investigation concerning the ligand-to-rhodium ratio, however, Lemaire and co-workers postulated that the active catalyst is most likely a rhodium complex having only one diamine ligand coordinated to the metal atom.[36] The ligand-to-metal ratio was varied in a range from 1 to 5 equiv, using ligands **1d**, **6d**, **12b**, and **18** in the iridium(I)-catalyzed reduction of acetophe-

(36) Bernard, M.; Guiral, V.; Delbecq, F.; Fache, F.; Sautet, P.; Lemaire, M. *J. Am. Chem. Soc.* **1998**, *120*, 1441−1446.

Table 5. Hydrogen Transfer Reduction of Acetophenone Using Various Ligand:Iridium Ratios[a]

entry	ligand	ligand:Ir	conv. (0.5 h) (%)[b]	ee (%)[c]	confign
1	**1d**	1:1	73	–	–
2	**1d**	2.5:1	90	–	–
3	**1d**	5:1	91	–	–
4	**6d**	1:1	64	9	*S*
5	**6d**	2.5:1	70	12	*S*
6	**6d**	5:1	82	12	*S*
7	**12b**	1:1	61	65	*S*
8	**12b**	2.5:1	99	65	*S*
9	**12b**	5:1	99	65	*S*
10	**18**	1:1	44	60	*S*
11	**18**	2.5:1	45	65	*S*
12	**18**	5:1	47	65	*S*

[a] The reaction was performed at 60 °C using 4 mmol of substrate in 3 mL of a formic acid/triethylamine (5:2) solution. Substrate:[IrCl(COD)]$_2$:ligand = 400:1:2−10. [b] Conversions were determined by GLC analysis. [c] Determined by capillary GLC analysis using a chiral cycloSil-B column.

Table 6. Hydrogen Transfer Reduction of Acetophenone at Various Temperatures[a]

entry	ligand	*T* (°C)	conv. (%) (time (h))[b]	ee (%)[c]	confign
1	**6d**	60	98 (1)	12	*S*
2	**6d**	40	24 (1)	19	*S*
3	**6d**	20	15 (5)	19	*S*
4	**12b**	60	99 (1)	65	*S*
5	**12b**	40	38 (1)	67	*S*
6	**12b**	20	57 (5)	80	*S*
7	**18**	60	50 (1)	58	*S*
8	**18**	40	12 (1)	69	*S*
9	**18**	20	11 (5)	69	*S*

[a] The reaction was performed at the indicated temperature using 4 mmol of substrate in 3 mL of a formic acid/triethylamine (5:2) solution. Substrate:[IrCl(COD)]$_2$:ligand = 400:1:5. [b] Conversions were determined by GLC analysis. [c] Determined by capillary GLC analysis using a chiral cycloSil-B column.

none. When the ligand-to-metal ratio was changed from 1 to 2.5, both the activity and enantioselectivity increased only slightly (Table 5). This is most likely due to enhanced stabilization of the iridium complex, prohibiting the formation of unsaturated iridium species that might lead to racemic phenyl ethanol.[36] Addition of more than 2.5 equiv of ligand did not affect the outcome of the reaction any further.

Influence of the Reaction Temperature. The effect of the temperature on the enantioselectivity of the reaction was tested using ligands **6d**, **12b**, and **18**. Decreasing the reaction temperature in a range from 60 to 20 °C resulted in an increase in the enantioselectivity in all cases (Table 6). Using the diastereomer *S*-benzyl-(*R*)-cysteinol (*R*)-sulfoxide (**12b**) as a ligand, the largest difference in enantioselectivity was observed, ranging from 65% ee at 60 °C to 80% ee at 20 °C (entries 4−6, Table 6). In the case of ligand **18**, the beneficial temperature effect also resulted in a marked difference in enantioselection (entries 7−9, Table 6).

Influence of the Hydrogen Source. An alternative hydrogen source for the azeotropic mixture of formic acid and triethylamine is 2-propanol. The results of the experiments using 2-propanol as a hydrogen donor in iridium(I)-catalyzed reduction of acetophenone with various *N*,*S*-chelates are presented in Table 7. Using the amino-acid-based aminosulf(ox)ides (**6d** and **12b**), the initial product configuration proved to be *R*. At higher conversions, the product configuration changed to *S*, as

Table 7. Hydrogen Transfer Reduction of Acetophenone Using 2-Propanol as a H Donor[a]

entry	ligand	time (h)	conv. (%)[b]	ee (%)[c]	confign
1	**6d**	1/20	7/45	33/33	*R*/*S*
2	**12b**	1/20	6/24	16/13	*R*/*S*
3[d]	**6d**	1/20	2/15	19/18	*S*/*S*
4	**16**	1	83	24	*R*
5	**17**	1	88	73	*S*
6	**18**	1	96	65	*S*
7	**19**	1	40	2	*R*
8	**20**	1	82	**80**	*R*
9	**21**	1	22	**82**	*S*
10	**22a**	1	85	39	*R*

[a] The reaction was performed at 20 °C using 4 mmol of substrate in a 0.1 M 2-propanol solution. Substrate:[IrCl(COD)]$_2$:ligand:*t*BuOK = 400:1:5:12.5. [b] Conversions were determined by GLC analysis. [c] Determined by capillary GLC analysis using a chiral cycloSil-B column. [d] In situ catalyst incubation time = 30 min.

shown in Table 7. The change in product configuration during the reaction is most likely due to a change in the ligand coordination fashion. Under the basic reaction conditions, the alcohol functionality is deprotonated, resulting in ligand coordination involving nitrogen and oxygen donor atoms instead of nitrogen and sulfur. The experiment described in entry 1 was repeated using a longer incubation time of the in situ catalyst. After addition of the basic cocatalyst (i.e., *t*BuOK), the reaction mixture was stirred for 30 min before adding the substrate (entry 3, Table 7). This resulted in an *S* product configuration that was constant in time. Both the catalyst activity and selectivity dropped when longer incubation times were used.

Using the aminosulfides derived from (nor)ephedrine and 2-aminodiphenylethanol (**16**−**22a**), the reaction rates and the enantioselectivities substantially increased with 2-propanol as the H-donor instead of formic acid. Ligand **20** induced 80% ee using 2-propanol as the hydrogen source. As was also found with formic acid as the hydrogen donor (see also Table 3), the product configuration changed to *R* when more bulky phenyl substituents were introduced. However, the system using 2-propanol seems to be more sensitive to this change in ligand structure, as suggested by the fact that the product configuration changed to *R* also in the cases of ligands **16**, **20**, and **22a**, in contrast to the results obtained with the system using formic acid as the H-donor. The change in product configuration can only be explained by different catalytic intermediates in the enantioselectivity-determining step.

Mechanistic Considerations. From a mechanistic point of view, two general pathways can be envisaged for transfer hydrogenation (Figure 2): a stepwise process through a hydride complex (the "hydridic route", path A) and a concerted process in which the hydrogen is directly transferred from the hydrogen donor to the substrate ("direct hydrogen transfer", path B).[24]

For transition-metal-catalyzed transfer hydrogenation, some key features have been discovered that support the hydridic route (path A). Noyori and co-workers[37] showed that the structure of the supposed active species in ruthenium(II)-catalyzed transfer hydrogenation is a ruthenium(II) 16-electron complex bearing TsDPEN as the ligand and an η^6-arene moiety. In the presence of 2-propanol, an 18-electron *ruthenium hydride* species is formed

(37) Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285−288.

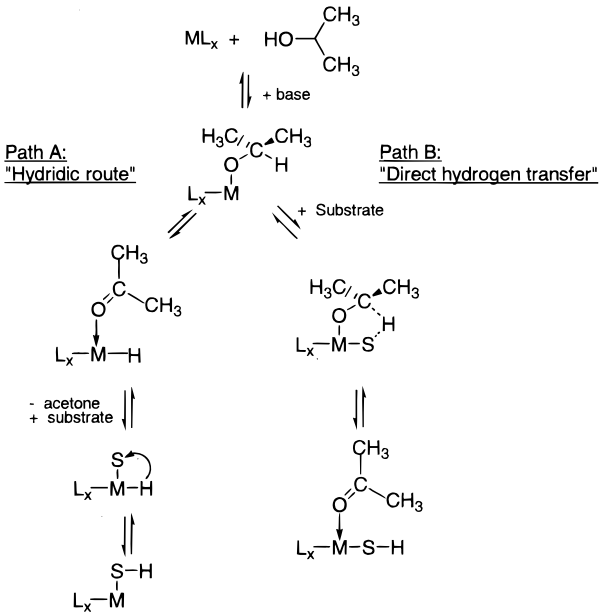
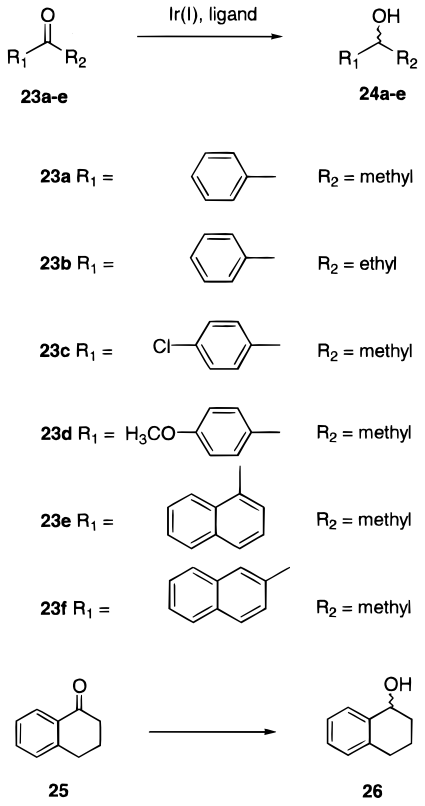


Figure 2. Two mechanistic pathways for hydrogen transfer reactions.

that catalyzes the reduction of various ketones. Isolation of these complexes confirms that the ruthenium-catalyzed transfer hydrogenation takes place by way of a metal hydride rather than a metal alkoxide, as is active in the Meerwein−Ponndorf−Verley reduction. Lemaire and co-workers[36] showed that the active complex in rhodium(I)-catalyzed transfer hydrogenation is most likely a *rhodium hydride* complex with one diamine and one diene coordinated to the metal. When the active catalyst is presumed to be a metal hydride, the enantioselective outcome of the reaction is expected to be independent of the hydrogen donor that is involved. However, it should be noted that solvent effects can also give rise to differences in the enantioselective outcome of the reaction.

The results presented in Tables 3 and 7 show that the enantioselectivity of the reaction is largely affected by the use of different hydrogen donors. Therefore, a mechanistic route in which the hydrogen is transferred to the substrate in a concerted process cannot be excluded. Enantiomer-discriminating H-transfer reactions via the direct hydrogen transfer mechanism can give rise to different enantioselectivities using various hydrogen donors. In the examples shown here (Table 3 versus Table 7), a large difference in enantioselectivity is observed when changing the H-donor, even resulting in the opposite product configurations in some cases. In addition, Noyori and co-workers[1] showed that the presence of a NH moiety in the ligand is of crucial importance in obtaining high activities and enantioselectivities. It was therefore proposed that the ruthenium(II)-catalyzed transfer hydrogenation occurs by hydrogen bond formation between the NH linkage of the amine ligand and the carbonyl functionality of the substrate.[1] In the transition state, a six-membered ring is formed, after which both the metal hydride and the amine proton of the ligand are donated to the substrate (so-called bifunctional catalysis). DFT calculations on possible catalytic intermediates confirmed this hypothesis.[38] However, for iridium(I)- and rhodium(I)-catalyzed hydrogen transfer reactions, this theory proved to be inconsistent. Using the latter two metal catalysts in combination with

Scheme 9. Asymmetric Transfer Hydrogenation of Ketones 23a−25



diimine-type ligands (e.g., bipyridines, phenanthrolines, and bioxazoles) lacking an amine proton, the reduction of ketones is successful as well.[3,24]

In summary, the enantioselective outcome of the reaction in the iridium(I)-catalyzed transfer hydrogenation is strongly influenced by the type of hydrogen donor (i.e., formic acid or 2-propanol). This change in enantioselectivity might be caused by the interference of a direct hydrogen transfer path (path B, Figure 2), resulting in a different catalytic intermediate in the enantioselectivity-determining step of the reaction.

Variations of the Substrate. To investigate the scope of the transfer hydrogenation systems presented above, ketones other than acetophenone (**23a**) were subjected to reduction using ligands **12b**, **18**, and **20** (see Scheme 9). The results are presented in Table 8. The enantioselective outcome of the reaction was significantly influenced by the electronic and steric properties of the substrate. The enantioselectivity increased when the substrate contained more steric bulk, as in **23b**, **23e**, and **23f**. An electron-withdrawing substituent in the substrate (**23c**) resulted in a higher enantioselectivity, whereas an electron-donating substituent (**23d**) gave rise to a lower ee. An exception to the trend is the rigid and bulky ketone α-tetralone (**25**). Reduction of this substrate resulted in moderate enantioselectivities of the corresponding alcohol (**26**), which might be due to the fixed ring conformation of this substrate.

The use of 2-propanol as a hydrogen donor in the asymmetric transfer hydrogenation of acetophenone is

(38) (a) Alonso, D. A.; Brandt, P.; Nordin, S. J. M.; Andersson, P. G. *J. Am. Chem. Soc.* **1999**, *121*, 9580−9588. (b) Petra, D. G. I.; Reek, J. N. H.; Handgraaf, J.-W.; Meijer, E. J.; Dierkes, P.; Kamer, P. C. J.; Brussee, J.; Schoemaker, H. E.; Van Leeuwen, P. W. N. M. *Chem.−Eur. J.* Manuscript accepted.

Table 8. Hydrogen Transfer Reduction of Ketones 23a−f and 25

entry	ketone	ligand	H donor	conv. (1 h) (%)[c]	ee (%)[d]	confign
1	**23a**	**12b**	HCOOH[a]	99	65	*S*
2	**23a**	**18**	HCOOH[a]	>99	65	*S*
3	**23a**	**20**	*i*PrOH[b]	82	80	*R*
4	**23b**	**12b**	HCOOH[a]	82	73	*S*
5	**23b**	**18**	HCOOH[a]	92	77	*S*
6	**23b**	**20**	*i*PrOH[b]	95	92	*R*
7	**23c**	**12b**	HCOOH[a]	>99	52[e]	*S*
8	**23c**	**18**	HCOOH[a]	97	52[e]	*S*
9	**23c**	**20**	*i*PrOH[b]	99	77[e]	*R*
10	**23d**	**12b**	HCOOH[a]	95	65	*S*
11	**23d**	**18**	HCOOH[a]	80	65	*S*
12	**23d**	**20**	*i*PrOH[b]	52	88	*R*
13	**23e**	**12b**	HCOOH[a]	>99	79	*S*
14	**23e**	**18**	HCOOH[a]	>99	79	*S*
15	**23e**	**20**	*i*PrOH[b]	99	97	*R*
16	**23f**	**12b**	HCOOH[a]	>99	70	*S*
17	**23f**	**18**	HCOOH[a]	>99	59	*S*
18	**23f**	**20**	*i*PrOH[b]	97	87	*R*
19	**25**	**12b**	HCOOH[a]	98	55	*S*
20	**25**	**18**	HCOOH[a]	92	55	*S*
21	**25**	**20**	*i*PrOH[b]	39	37	*R*

[a] The reaction was performed at 60 °C using 4 mmol of substrate in 3 mL of a formic acid/triethylamine (5:2) solution. Substrate:[IrCl(COD)]$_2$:ligand = 400:1:5. [b] The reaction was performed at 20 °C using 4 mmol of substrate in a 0.1 M 2-propanol solution. Substrate:[IrCl(COD)]$_2$:ligand:*t*BuOK = 400:1:5:12.5. [c] Conversions were determined by GLC and/or 300-MHz ^{1}H NMR analysis. [d] Determined using chiral HPLC analysis with a Chiracel OD column, unless otherwise specified. [e] Determined by capillary GLC analysis using a chiral cycloSil-B column.

restricted by the fact that the reaction must be performed using a substrate concentration as low as 0.1 M, because of the structural similarities of the product alcohol and the H-donor.[1] To become economically feasible, the reaction should be performed using higher substrate concentrations and consequently less 2-propanol. The effect of different substrate concentrations was investigated using ligand **20** in the iridium(I)-catalyzed reduction of acetophenone (**23a**) and 1′-acetonaphthone (**23e**). Table 9 shows that a higher substrate concentration of up to 0.3 M does not significantly affect the enantioselective outcome of the reaction.

Concluding Remarks

Two series of *N*,*S*-chelates were synthesized that were very effective as a new class of ligands for the iridium-(I)-catalyzed transfer hydrogenation of prochiral ketones. Both the sulfoxide-containing β-amino alcohol (**12b**) and the aminosulfides derived from 1,2-disubstituted amino alcohols (**16**−**21**) gave rise to high reaction rates and moderate to excellent enantioselectivities in the reduction of various ketones. The enantioselective outcome of the reaction was directed by selecting the appropriate ligand and hydrogen donor. Depending on the ligand structure and stoichiometry, the substrate, the reaction temperature, and the hydrogen donor, enantioselectivities of up to 97% could be reached. The best results were obtained with the aminosulfide ligand (1*S*,2*R*)-2-amino-1,2-diphenyl-1-benzylthioethane (**20**), which turned out to be a good ligand for the control of asymmetric iridium-catalyzed transfer hydrogenation of prochiral ketones.

Table 9. Hydrogen Transfer Reduction Using Ligand 20 in 2-Propanol at Different Substrate Concentrations[a]

entry	ketone	conc. (M)	conv. (h) (%)[b] (time (h))	ee (%)[c]	confign
1	**23a**	0.1	82 (1)	80[d]	*R*
2	**23a**	0.2	92 (0.5)	82[d]	*R*
3	**23a**	0.3	94 (0.5)	81[d]	*R*
4	**23e**	0.1	99 (1)	97	*R*
5	**23e**	0.2	99 (1)	96	*R*

[a] The reaction was performed at 20 °C using 4 mmol of substrate in a 2-propanol solution. Substrate:[IrCl(COD)]$_2$:ligand:*t*BuOK = 400:1:5:12.5. [b] Conversions were determined by GLC and/or 300-MHz ^{1}H NMR analysis. [c] Determined using chiral HPLC analysis with a Chiracel OD column, unless otherwise specified. [d] Determined by capillary GLC analysis using a chiral cycloSil-B column.

Acknowledgment. Financial support from the Innovation Oriented Research Program (IOP-Katalyse) is gratefully acknowledged. Wim G. J. de Lange is acknowledged for technical assistance.

Supporting Information Available: Experimental details; characterization data for compounds **6e**−**22b**; IR, ^{1}H NMR, ^{13}C NMR, HRMS, and elemental analysis data; GC and HPLC conditions for the separation of the enantiomers of **24a**−**26**, as well as crystal structure refinement data for compound **12a**, including atomic coordinates, isotropic and anisotropic displacement parameters, and a listing of bond angles and bond lengths. This material is available free of charge via the Internet at http://pubs.acs.org.

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