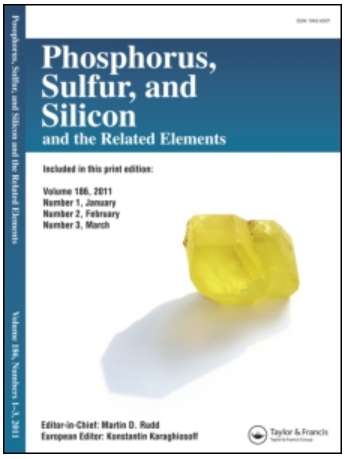

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CHIRAL DIFERROCENYL DICHALCOGENIDES IN ASYMMETRIC SYNTHESIS

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Our recent studies on asymmetric synthesis using chiral organochalcogen (S, Se, Te) compounds are presented. A variety of chiral diferrocenyl dichalcogenides have been newly prepared, some of which being employed as reagents for new asymmetric reactions such as selenoxide elimination, [2,3]sigmatropic rearrangement of chiral selenoxides, selenimides and tellurimides, and intramolecular selenenylation of alkenes. These dichalcogenides, as well as several newly prepared chiral ferrocenyl monochalcogenides, also act as chiral ligands in the rhodium- and iridium-catalyzed asymmetric hydrosilylation and transfer hydrogenation of ketones.

KEYWORDS: selenoxide, selenimide, tellurimide, chiral diferrocenyl dichalcogenide, chiral ligand, hydrosilylation

1. INTRODUCTION

A variety of characteristic and useful organic reactions using organochalcogen (S, Se, Te) compounds have been revealed, but their application to asymmetric organic synthesis is still undeveloped especially in the cases of Se and Te. We are interested in the

introduction of asymmetric methodology to the branch of Se and Te chemistry because it may be possible to obtain, even if *in situ*, optically active organochalcogen compounds having a chiral center on a chalcogen atom. For this purpose, we undertook to introduce a chiral ferrocenyl group as an aryl moiety of arylchalcogen compounds, since the compounds having a ferrocene planar chirality, such as chiral ferrocenyl phosphines, are known to be very important in the field of catalytic asymmetric synthesis.[1] We eventually succeeded in the preparation of a variety of chiral diferrocenyl dichalcogenides and ferrocenyl monochalcogenides and developed several new asymmetric organic reactions using these compounds as reagents as well as chiral ligands. Here, some of our recent results on this subject are presented.[2]

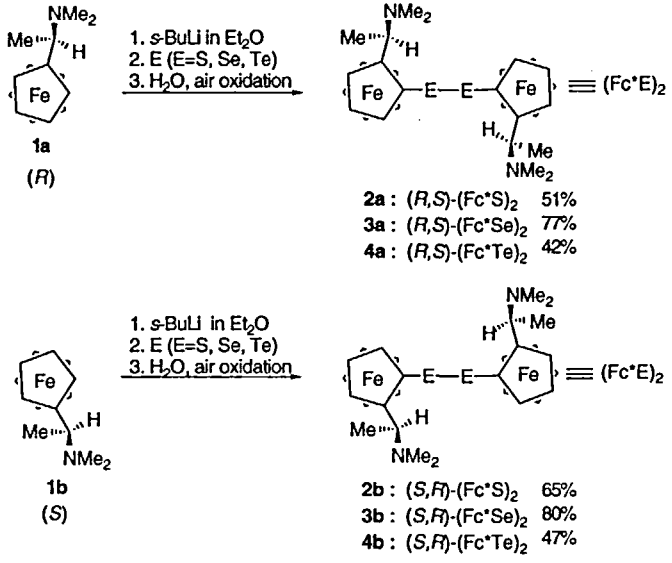
2. NOVEL CHIRAL DIFERROCENYL DICHALCOGENIDES, THEIR DERIVATIVES, AND THEIR CRYSTAL STRUCTURES[3-6]

We first prepared six optically active [*R,S;R,S*]- and [*S,R;S,R*]-bis[2-[1-(dimethylamino)ethyl]ferrocenyl] dichalcogenides and elucidated some of their structures by X-ray crystallography.

Treatment of commercial (*R*)-(1-dimethylaminoethyl)ferrocene with *sec*-butyllithium followed by addition of elemental selenium and air oxidation afforded a diastereomeric mixture of bis[2-[1-(dimethylamino)ethyl]ferrocenyl] diselenides which mostly consisted of [*R,S;R,S*]-isomer,[3] in accordance with the reported[7] highly diastereoselective lithiation [94% diastereomeric excess(de)] of the ferrocene. After one column chromatographic purification, pure [*R,S;R,S*]-diselenide **3a** was obtained in 77% yield as a red solid of $[\alpha]_D$ -650 (Scheme 1).

Similarly, starting from commercial (*S*)-(1-dimethylaminoethyl)ferrocene, the corresponding pure [*S,R;S,R*]-diselenide **3b** was prepared in 80% yield as a red solid of $[\alpha]_D$ +650. The corresponding sulfur and tellurium analogues {[*R,S;R,S*]- and [*S,R;S,R*]-$(Fc^*E)_2$ (E=S, Te)} (**2** and **4**, respectively) were similarly obtained from (*R*)- and (*S*)-(1-dimethylaminoethyl)ferrocenes **1** as an orange solid (51-65%) and a black solid (42-47%), respectively (Scheme 1).[4,5] All these dichalcogenides are stable in air and can be stored for a long time in nitrogen. The structures of **2b** and **3b** were fully characterized by X-ray crystallography and the absolute configuration was clarified to be *S*, *R*, where the configuration around the ferrocene axis is *R* (Figs. 1 and 2).

Scheme 1



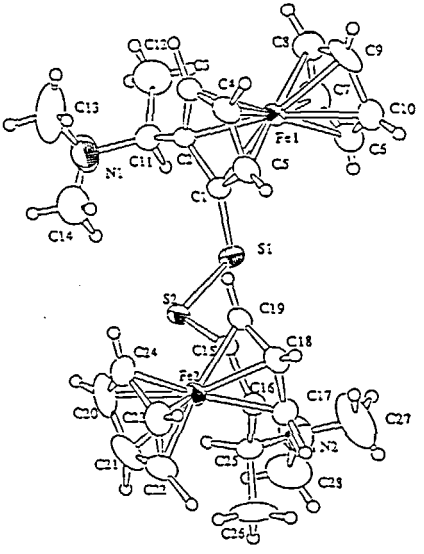


Figure 1. Crystal structure of **2b**.

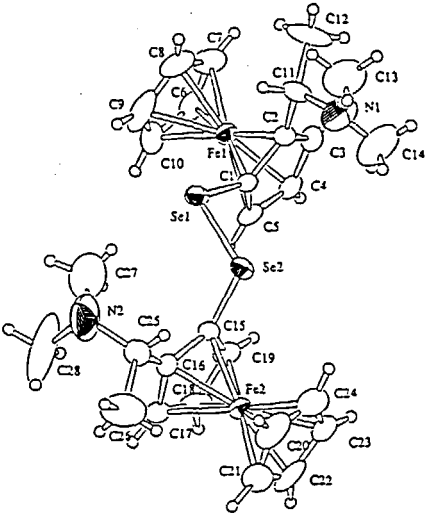


Figure 2. Crystal structure of **3b**.

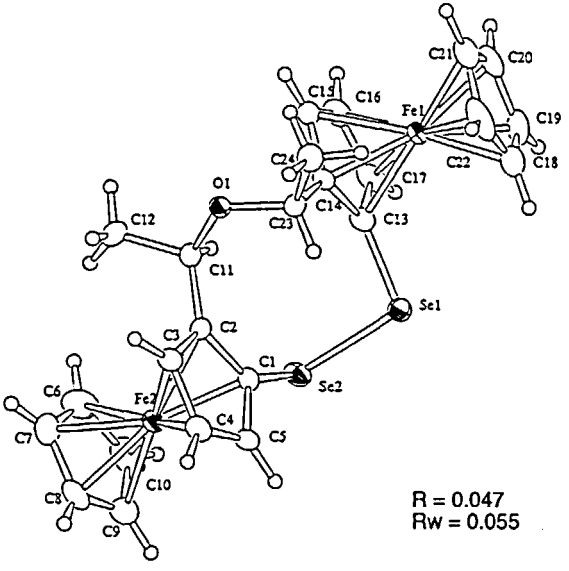
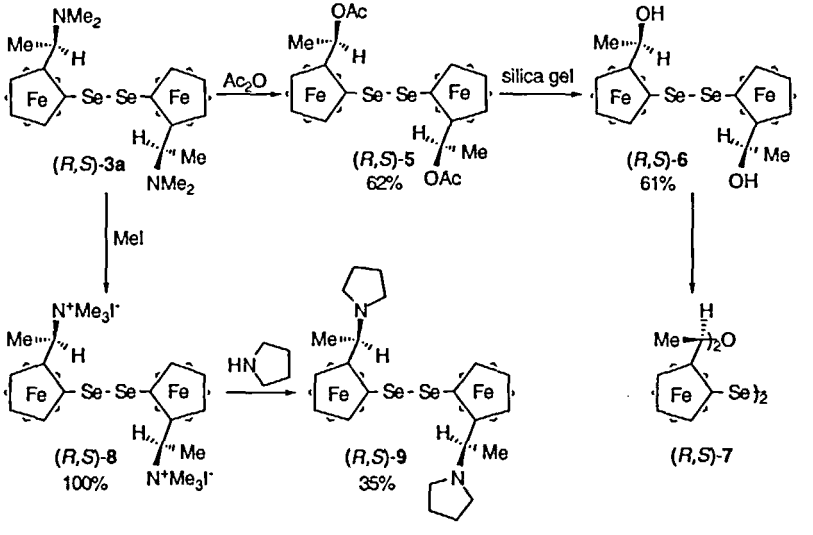


Figure 3. Crystal structure of **7**.

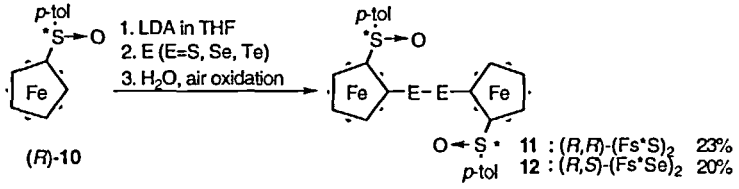
We next prepared a variety of chiral diferrocenyl diselenides from (*R,S*)-**3** through several transformations as shown in Scheme 2. A slow recrystallization of the diselenide **6** from CH_2Cl_2 at room temperature afforded a diselenide having a nine-membered ring **7** as an orange solid and its structure was fully characterized by X-ray crystallography (Figure 3).

Scheme 2



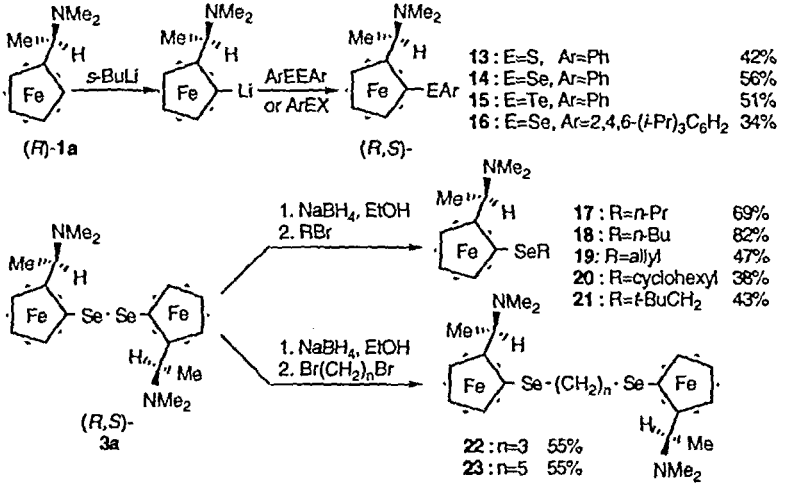
Novel dichalcogenides having a chiral sulfoxide moiety on the ferrocene ring was also prepared as shown in Scheme 3. Treatment of (*R*)-ferrocenyl *p*-tolyl sulfoxide **10**, which can be prepared easily by the Anderson method,[8] with lithium diisopropylamide (LDA) at -78 °C followed by addition of elemental sulfur or selenium and air oxidation afforded an enantiomeric mixture of bis[2-(*p*-tolylsulfinyl)ferrocenyl] disulfide **11** or the diselenide **12**, which consisted mostly of (*R,S*)-isomer in accordance with the reported high diastereoselective lithiation (>99% de)[8] of the ferrocene.

Scheme 3



On the other hand, new monochalcogenides **13-23** were prepared as shown in Scheme 4. Treatment of (*R*)-(1-dimethylaminoethyl)ferrocene **1a** with *sec*-butyllithium followed by reaction with diphenyl disulfide afforded an enantiomeric mixture of (1-dimethylaminoethyl)ferrocenyl phenyl sulfide which consisted mostly of (*R,S*)-isomer, and the purification by column chromatography using SiO_2 gave (*R,S*)-sulfide **13** in a pure form in 42% yield. Similarly, other chiral aryl ferrocenyl chalcogenides such as (*R,S*)-ferrocenyl phenyl selenide **14** and the telluride **15** and (*R,S*)-ferrocenyl 2,4,6-triisopropylphenyl selenide **16** were prepared by the reaction with the corresponding diphenyl dichalcogenides and 2,4,6-triisopropylphenylselenenyl bromide in 56%, 51% and 34% yields, respectively. Novel (*R,S*)-alkyl ferrocenyl selenides **17-21** were prepared by the reaction of chiral ferrocenylselenide anion derived from **3a** with the corresponding alkyl halides in 38-82% yield. When the anion derived from **3a** was reacted with 1,3-dibromopropane (n=3) and 1,5-dibromopentane (n=5), [*R,S;RS*]-alkanes possessing two ferrocenylselenium moieties such as **22** and **23** were produced, both in 55% yield.

Scheme 4

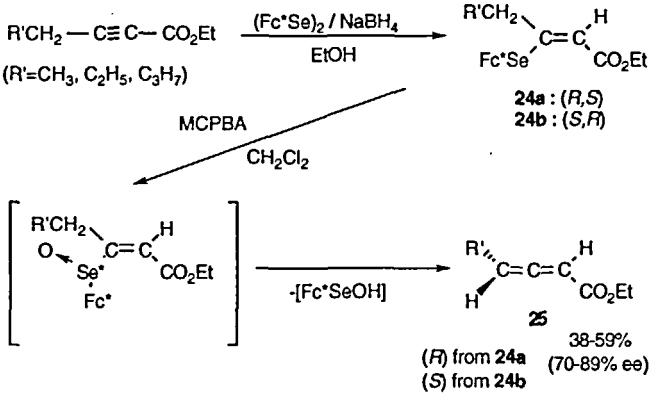


3. APPLICATION TO ASYMMETRIC SYNTHESIS AS REAGENTS

3.1 Asymmetric Selenoxide Elimination Leading to Chiral Allenecarboxylic Esters[3)]

The oxidation of vinyl selenides **24** was carried out with 1 mol equiv. of *meta*-chloroperbenzoic acid (MCPBA) under various conditions. The chiral selenoxides formed underwent *in situ* selenoxide elimination to afford axially chiral allenecarboxylic esters **25** in moderate chemical yields with high enantioselectivities (Scheme 5). Chiral selenoxides, key intermediates in this asymmetric reaction, are known to racemize easily with even a small amount of water and, in fact, the addition of molecular sieve 4Å to the reaction system greatly improved the stereoselectivity.

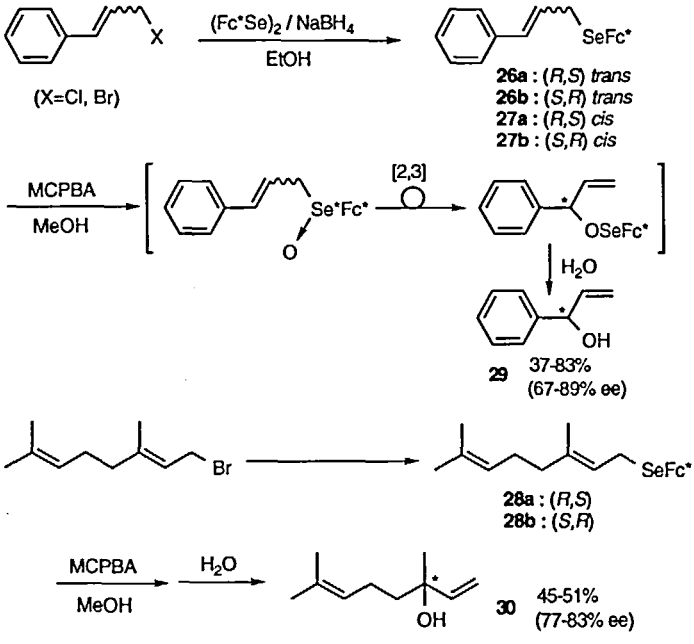
Scheme 5



3.2 Asymmetric [2,3]Sigmatropic Rearrangement of Chiral Selenoxides Leading to Chiral Allylic Alcohols[3)]

Treatment of chiral allylic ferrocenyl selenides **26-28** with 1 mol equiv. of MCPBA at 0 °C or -78 °C for 1 h in various solvents afforded the corresponding optically active allylic alcohols **29** and **30** in moderate to good chemical yields with high enantioselectivities (Scheme 6). In contrast to the oxidation of vinylic selenides described above, the reaction temperature did not exert any marked effect on the stereochemical result, and methanol was the solvent of choice. The fact that methanol could be used for obtaining a high enantiomeric excess (ee) value indicates a fast sigmatropic rearrangement of the intermediate chiral ferrocenyl selenoxides, since it is known that racemization of optically active selenoxides occurs readily in methanol.

Scheme 6

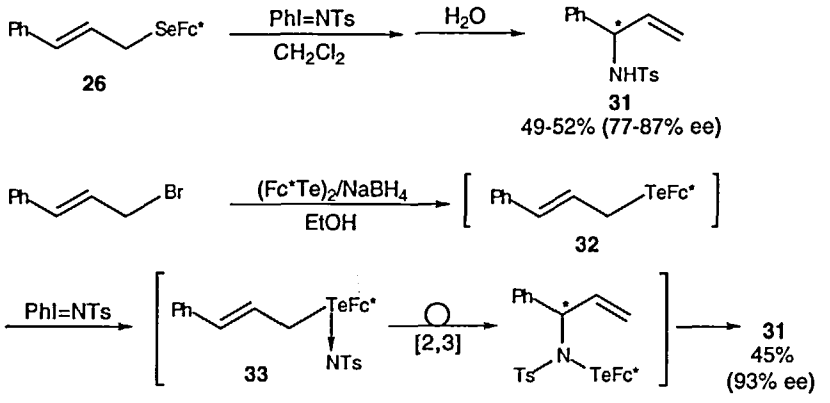


3.3 Asymmetric [2,3]Sigmatropic Rearrangement of Chiral Selenimides and Tellurimides Leading to Chiral Allylic Almines[9,10]

The selenimides, which are nitrogen analogues of selenoxides, are known to undergo the same [2,3]sigmatropic transformation as selenoxides. On the other hand, the chemical behavior of tellurimide analogues has not yet been investigated at all. We succeeded in the asymmetric imination of chiral cinnamyl ferrocenyl selenides (**26**) and tellurides (**32**) with [N-(p-toluenesulfonyl)imino]phenyliodinane (PhI=NTs) to afford the corresponding chiral allylic amines (**31**) (Scheme 7). These reactions may proceed via highly diastereoselective imination on Se and Te atoms and [2,3]sigmatropic

rearrangement of the produced selenimides and tellurimides (**33**) almost without loss of optical purity.

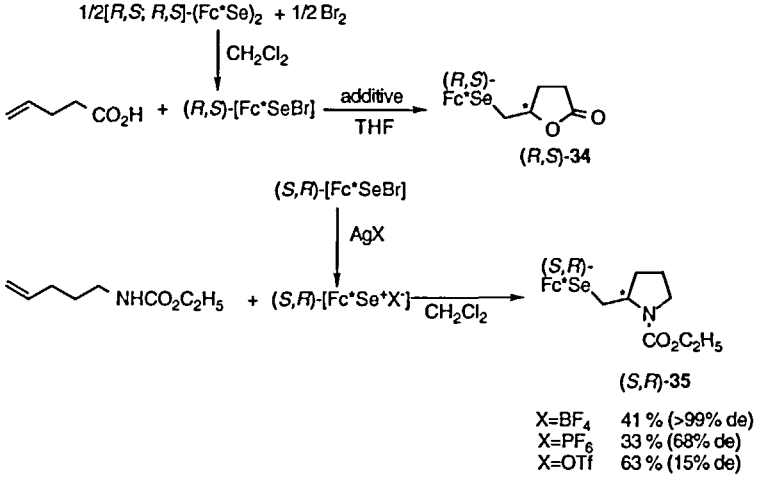
Scheme 7



3.4 Asymmetric Intramolecular Selenenylaion of Alkenes[11]

Asymmetric intramolecular selenocyclization of alkenoic acids, alkenols and olefinic urethanes using chiral ferrocenylselenenyl cations proceeded smoothly to give the corresponding lactones, cyclic ethers and *N*-heterocyclic compounds, respectively, in moderate chemical yields with very high diastereoselectivities. In sharp contrast to intermolecular selenenylation, the presence of triethylamine was essential for obtaining a cyclic product such as **34** in high chemical yield from alkenoic acids and alkenols (Scheme 8). The counteranion of the chiral ferrocenylselenenyl moiety played an important role in the stereoselection of the resultant *N*-heterocyclic compound **35** (Scheme 8). This method might be useful for preparing chiral heterocyclic compounds.

Scheme 8



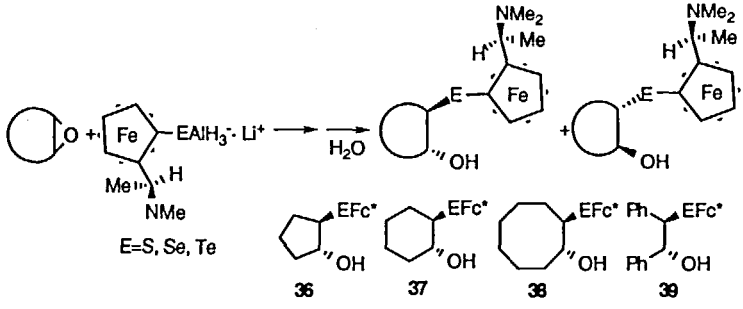
3.5 Asymmetric Nucleophilic Ring Opening of meso-Epoxides

In order to elucidate how these newly prepared dichalcogenides are able to differentiate molecules stereochemically in nucleophilic reactions, we adopted a nucleophilic ring opening reaction of meso-epoxides using these chiral ferrocenylchalcogenide anions, and succeeded in obtaining ferrocenyl β-hydroxyalkyl chalcogenides in high yields with high de values.

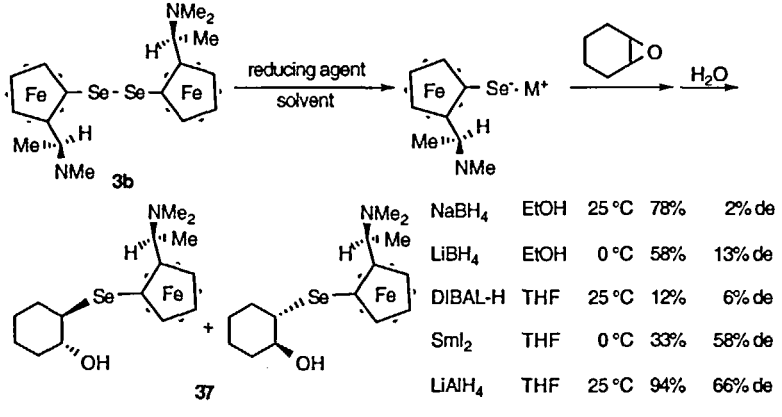
The yield of ring opening products (**36-39**) was quite high (77-97% yield) irrespective of the kind of chalcogen atom and epoxide, but the de value greatly depended on them (Scheme 9). The reaction of cyclopentene oxide with a nucleophile of the larger chalcogen atom resulted in lower selectivities (S > Se > Te; 71, 44 and 41% de, respectively). In the cases of cyclooctene oxide and *cis*-stilbene oxide, similar tendencies were observed (cyclooctene oxide, S ≈ Se > Te; 40, 43 and 21% de: *cis*-stilbene oxide, S > Se > Te; 45, 33 and 13% de). These results may be explained by considering the

distance between the chalcogenide anion (reaction site) and the chiral part, wherein a shorter distance favors the higher de (S > Se > Te). On the other hand, the result of cyclohexene oxide was different from those of others. The use of diselenide gave the best result (66% de), and with disulfide and ditelluride the selectivity was quite low (10 and 8% de). The reason for this substrate selectivity is not yet clear. Diastereoselectivity also depended on the kind of reducing agent, as shown in Scheme 10; the strongest reducing reagent $LiAlH_4$ gave the best result.

Scheme 9



Scheme 10

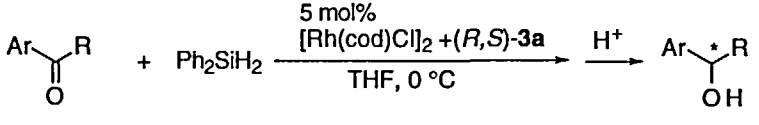


4. APPLICATION TO ASYMMETRIC SYNTHESIS AS CHIRAL LIGANDS

4.1 Rh- and Ir-Catalysed Asymmetric Hydrosilylation of Ketones [5]

We envisaged to use these newly prepared organochalcogen compounds as chiral ligands for transition metal-catalysed asymmetric reactions. First, the effectiveness of these compounds was examined via Rh-catalysed hydrosilylation of acetophenone with diphenylsilane and it was eventually disclosed that these compounds work moderately as chiral ligands and also that the dichalcogenides (**2-4**) are generally more effective than monochalcogenides (**13-23**). Typical results of the reaction of a variety of alkyl aryl ketones with diphenylsilane in THF using $[Rh(cod)Cl]_2$-**3a** as a catalyst are shown in Scheme 11. A similar asymmetric hydrosilylation proceeded as well with iridium (I) complex, $[Ir(cod)Cl]_2$, but the enantioselectivity was lower (up to 23% ee).

Scheme 11

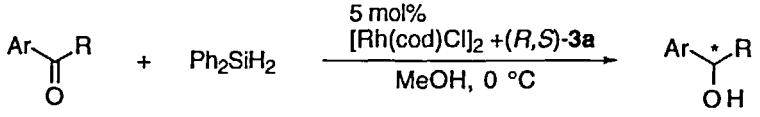


Ketone			Alcohol (*R*)	
Ar	R	Time (h)	GLC yield (%)	ee (%)
Ph	Me	24	31	85
Ph	Et	70	14	58
Ph	CH_2Cl	120	85	88
Ph	CO_2Me	25	31	60
Ph	*t*-Bu	240	5	85
indanone		240	5	42
p-$NO_2C_6H_4$	Me	72	45	76
p-ClC_6H_4	Me	72	41	74
2-thienyl	Me	96	100	78

4.2 Rh-Catalysed Asymmetric Transfer Hydrogenation of Ketones [12]

When similar reactions described in section 4.1 were carried out in methanol, the products were directly the chiral alcohols, not the hydrosilylated compounds. Typical results using $[Rh(cod)Cl]_2$ as a catalyst and **3a** as a chiral ligand are shown in Scheme 12. Here, the Rh (I) complex transfers hydrogen of methoxydiphenylsilane, $Ph_2Si(OMe)H$, to the carbonyl compound. The disulfides **2** and the ditellurides **3** were less effective for stereoselection.

Scheme 12



Ketone			Alcohol (*R*)	
Ar	R	Time (h)	GLC yield (%)	ee (%)
Ph	Me	70	46	48
Ph	Et	40	28	31
Ph	CH_2Cl	70	68	25
Ph	CO_2Me	25	95	41
Ph	*t*-Bu	170	11	95
indanone		170	15	31
p-$NO_2C_6H_4$	Me	50	92	25
p-ClC_6H_4	Me	70	51	22
p-$CH_3C_6H_4$	Me	70	0	—
p-$CH_3OC_6H_4$	Me	70	0	—
2-naphthyl	Me	70	24	37
2-thienyl	Me	70	100	43

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