A novel ferrocenyl diselenide for the catalytic asymmetric aryl transfer to aldehydes

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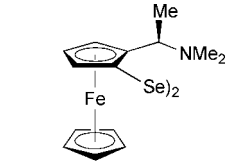
An oxazolinyl ferrocenyl diselenide was synthesised by directed *ortho*-metalation and used as catalyst precursor in the asymmetric addition of diethyl- and diphenylzinc to various aldehydes, yielding synthetically useful secondary alcohols, of which some are difficult to access using other catalytic methodologies. Enantioselectivities of up to 44% for the former and up to 85% for the latter transformations were obtained.

Organoselenium chemistry represents an established tool in organic synthesis.[1] However, compared to sulfur, this area is much less investigated, a fact that the reduced stability towards oxidative conditions and light as well as the frequently encountered toxicity of selenium reagents may account for. Extensive use of selenium in organic synthesis was initiated with the discovery of olefin formation by the decomposition of selenoxides, a reaction that proceeds under very mild conditions.[2] The chemistry of chiral selenium compounds is an even more undeveloped area.[3] Early articles dealing with their application in asymmetric catalysis were published in 1996 by Uemura and coworkers.[4] Ferrocene **1**, derived from Ugi's amine,[5] showed enantioselectivities of up to 88% in the rhodium(I)-catalysed hydrosilylation of ketones. This compound was also employed in the asymmetric transfer hydrogenation of ketones and in stoichiometric asymmetric syntheses like selenoxide eliminations,[6] [2,3]sigmatropic rearrangements[7] and intramolecular selenocyclisations.[8] Wirth *et al.*[9] demonstrated that **2** and related compounds are highly effective ligands in the asymmetric addition of diethylzinc to aromatic and aliphatic aldehydes.[10] With only 1 mol% of catalyst enantioselectivities of up to 98% were achieved for a wide range of substrates.

Recently, we developed a new catalytic system for the asymmetric addition of dialkylzinc reagents to aldehydes[11] based on 2-ferrocenyloxazoline, **3**, which is capable of inducing enantioselectivities up to 97% ee.[12] Even higher ee values were obtained in the analogous phenyl transfer reaction with a zinc reagent prepared *in situ* from diphenylzinc and diethylzinc,[12,13] leading to synthetically useful enantioenriched diarylmethanols with up to 98% ee.[14–16]



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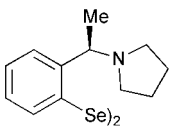

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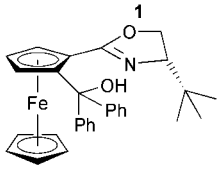

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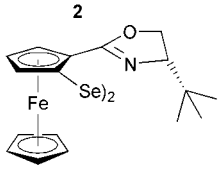

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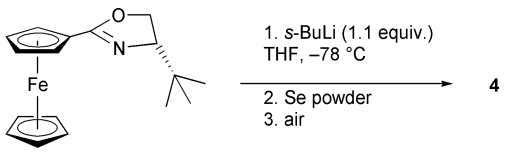
Encouraged by the fact that diselenide **2** displayed excellent selectivities in the alkylations, we assumed that compound **4** would also be useful for the asymmetric addition of diorganozinc reagents to aldehydes. Herein, we present the application of **4** as catalyst precursor in these reactions.

The synthesis of **4** was accomplished by directed *ortho*-lithiation[17] of (*S*)-2-ferrocenyl-4-*tert*-butyloxazoline **5**,[18] followed by addition of selenium powder (Scheme 1). Oxidation by air for several minutes afforded the diselenide in good yield (69%).

Initially, **4** was used in the addition of diethylzinc to aromatic and aliphatic aldehydes. The most significant results are summarised in Table 1. Although the results in the diethylzinc addition to aldehydes are highly unsatisfying ($ee_{max} = 44\%$ in the reaction with benzaldehyde), it is interesting to note that a structurally very similar compound, phenyloxazolinyl diselenide **6**,[9] devoid of the metal fragment, gives 1-phenylpropanol with only 8% ee in 1% yield.[19] The element of planar chirality present in **4** seems to have a decisive influence on both the enantioselectivity and yield of the reaction.[20]

Superior results were obtained in the asymmetric aryl transfer to aldehydes using a zinc reagent prepared by mixing diphenylzinc and diethylzinc in a 1 : 2 ratio. Compared to the addition of dialkylzincs, this reaction gave ee's of up to 85%



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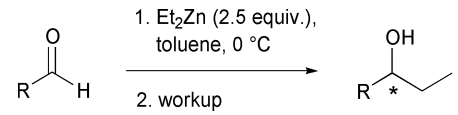
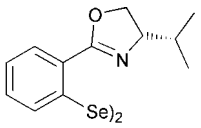
Scheme 1 Synthesis of ligand **4**

Table 1 Addition of diethylzinc to aldehydes in the presence of 2.5 mol% of **4**



Entry	R	Yield/%	ee/%	Abs. config.
1	Phenyl	68	44	*R*
2	4-Chlorophenyl	66	44	*R*
3	Hexyl	79	20	n.d.[a]

[a] n.d. = not determined.



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and uniformly high yields between 65 and 96% (Table 2). Aliphatic aldehydes were less suitable substrates, resulting in an enantiomeric excess of only 65% for 2,2-dimethyl-1-phenylpropanol. The catalytically active species is believed to be formed by heterolytic cleavage of the Se–Se bond of diselenide **4** (Scheme 2).[9]

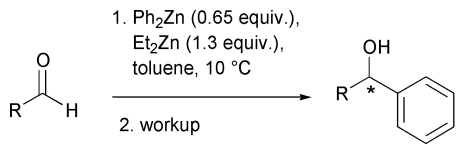
Most likely, zinc selenides such as **4a** or **4b** serve as catalysts. Based on the results by Wirth *et al.*[9] who demonstrated the inferiority of selenoethers in diethylzinc additions as concerns the rate and enantioselectivity compared to selenols, we believe that **4c** and **4d** play only a minor role in the stereochemical outcome of the catalysis.

In summary we have introduced a new catalyst for asymmetric addition reactions, capable of inducing moderate to high ee's with a zinc reagent prepared by mixing diethyl- and diphenylzinc. Further studies concerning the influence of the chalcogenide atom and the mechanistic details of the reaction are currently in progress.

Experimental

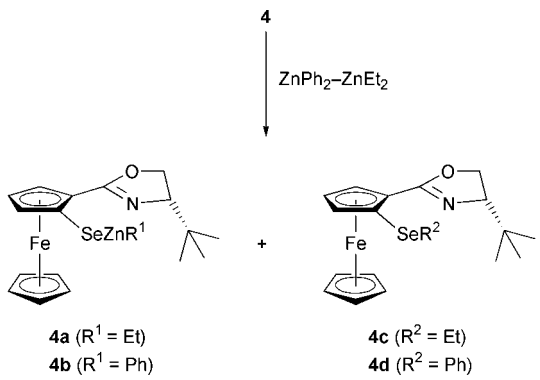
All manipulations except workup and purification were conducted under an inert atmosphere of Ar using standard Schlenk techniques. *s*-BuLi was purchased from Fluka as a 1.3 N solution in hexane. Diphenylzinc was obtained from Strem and handled in a glovebox under Ar. Tetrahydrofuran and toluene were distilled from sodium/benzophenone ketyl radical prior to use. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Gemini 300 spectrometer at 300 and 75 MHz, respectively, in $CDCl_3$, chemical shifts are given in ppm. All experiments were conducted at least twice to ensure reproducibility.

Table 2 Asymmetric phenyl transfer to aldehydes in the presence of 5 mol% of **4**



Entry	R	Yield/%	ee/%	Abs. config.
1	4-Chlorophenyl	85	84	*R*
2	2-Naphthyl	96	76	*R*
3	4-Biphenyl	86	85	*R*[a]
4	2-Bromophenyl	65	77	*R*
5	4-Tolyl	80	76	*R*[a]
6	*tert*-Butyl	85	65	*S*

[a] Tentatively assigned by assumption of an identical reaction pathway.



Scheme 2 Cleavage of the Se–Se bond in **4**

Preparation of compound 4

A solution of **5** (700 mg, 2.25 mmol) in 15 ml of THF is cooled to −78 °C and treated with *s*-BuLi (1.9 ml, 2.48 mmol). The resulting dark red solution is stirred for 30 min at this temperature, and then selenium powder (216 mg, 2.70 mmol) is added in one portion. The mixture is stirred for a further 10 min at −78 °C and subsequently warmed to room temperature within 15 min. After quenching with 30 ml of deionised water and extraction with dichloromethane (3 × 20 ml), air is bubbled through the combined organic layers for 5 min. The solution is dried over $MgSO_4$ and filtered. The solvent is evaporated and the product purified by column chromatography (pentane–diethyl ether, 2 : 1) to afford 600 mg of **4** as an orange solid (69% yield). Mp: 192 °C (dec.). $[\alpha]_D = -1270$ [c = 1.0, $CHCl_3$]. ^{1}H NMR: δ 1.05 (s, 18H), 3.99 (dd, J = 9.9 Hz, 7.4 Hz, 2H), 4.16 (s, 10H), 4.22–4.29 (m, 6H), 4.65–4.68 (m, 4H). ^{13}C NMR: δ = 25.9, 33.6, 69.2, 69.4, 70.2, 71.6, 72.0, 73.7, 76.7, 79.7, 165.2. MS (EI, 70 eV): m/z (%) 780.3 (7, M^+), 713.2 (6), 511.2 (16), 390.2 (100), 309.3 (35), 254.3 (38). IR (KBr): ν = 3435, 3108, 2956, 2186, 1655 cm^{-1}. Anal. calcd. for $C_{34}H_{40}Fe_2N_2O_2Se_2$: C, 52.47%; H, 5.18%; N, 3.60%; Found: C, 52.34%; H, 4.84%; N, 3.46%.

General procedure for the addition of diethylzinc to aldehydes

A solution of **4** (20 mg, 0.025 mmol) in toluene (2 ml) is treated with diethylzinc (0.25 ml, 2.5 mmol) at room temperature. After stirring for 30 min the dark orange solution is cooled to 0 °C and the aldehyde (1 mmol) is added neat in one portion. Stirring is continued at this temperature for 24 h, then the mixture is quenched by addition of a saturated aqueous solution of ammonium chloride (5 ml) and extracted with diethyl ether (3 × 10 ml). The collected organic layers are dried over $MgSO_4$ and the solvent is evaporated. The crude product is purified by column chromatography (pentane–diethyl ether) and subjected to HPLC or GLC analysis.

General procedure for the enantioselective phenyl transfer to aldehydes

In a glovebox a well-dried Schlenk flask is charged with diphenylzinc (36 mg, 0.16 mmol). The flask is sealed and removed from the glovebox. Freshly distilled toluene (3 ml) is added followed by diethylzinc (33 µl, 0.33 mmol). After stirring at room temperature for 30 min ferrocene **4** (10 mg, 0.013 mmol) is added, and then the resulting clear solution is cooled to 10 °C. Stirring is continued for an additional 10 min at this temperature; the aldehyde (0.25 mmol) is then added neat in one portion. The Schlenk flask is sealed and the reaction mixture stirred at 10 °C overnight. Quenching with water is followed by extraction of the mixture with diethyl ether. The combined organic layers are dried over $MgSO_4$ and the solvent is evaporated. The product is purified by column chromatography using silica gel (pentane–diethyl ether).

HPLC analysis: 1-phenyl-1-propanol [Chiralcel OD-H, heptane–Pr^{i}OH = 96 : 4, 0.5 ml min^{-1}, (*R*): 16.7, (*S*): 18.7 min]; 1-(4-chlorophenyl)-1-propanol [Chiralcel OD, heptane–Pr^{i}OH = 97 : 3, 0.5 ml min^{-1}, (*S*): 23.0, (*R*): 24.8 min]; α-(4-chlorophenyl)phenylmethanol [Chiralcel OB, heptane–Pr^{i}OH = 80 : 20, 0.8 ml min^{-1}, (*R*): 8.8, (*S*): 13.3 min]; α-(2-naphthyl)phenylmethanol [Chiralcel OD, heptane–Pr^{i}OH = 90 : 10, 0.8 ml min^{-1}, (*S*): 20.4, (*R*): 23.7 min]; α-(4-biphenyl)phenylmethanol [Chiralcel OD, heptane–Pr^{i}OH = 98 : 2, 1.0 ml min^{-1}, (*R*): 65.9, (*S*): 75.5 min]; α-(2-

bromophenyl)phenylmethanol [Chiralcel OD, heptane–Pr^iOH = 90 : 10, 0.9 ml min^{-1}, (*R*): 11.6, (*S*): 14.9 min]; α-(4-tolyl)phenylmethanol [Chiralcel OB, heptane–Pr^iOH = 98 : 2, 0.9 ml min^{-1}, (*S*): 35.8, (*R*): 38.5 min]; 2,2-dimethyl-1-phenylpropanol [Chiralcel OD, heptane–Pr^iOH = 98 : 2, 1.0 ml min^{-1}, major: 11.0, minor: 16.7 min].

GLC analysis: 3-nonanol as trifluoroacetate derivative (Lipodex G; 50 m × 0.25 mm, 40–170 °C, minor: 93.5, major: 95.1 min).

Acknowledgements

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