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Synthesis of novel chiral 'salen-type' ferrocenyl ligands

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Abstract—Two novel chiral C_2-symmetrical ferrocenyl 'salen-type' ligands were prepared via reaction of suitable ferrocenyldiamines with 3,5-di-*tert*-butylsalicylaldehyde and tested in the asymmetric epoxidation of unfunctionalized alkenes. Although the asymmetric induction was quite low, an unusually high *trans*/*cis*-epoxide ratio and high reactivity of a *trans*-alkene substrate were observed.

1. Introduction

Enantioselective epoxidations are of great interest since chiral epoxides are important intermediates in the preparation of biologically active compounds, widely used in pharmaceutical and agricultural fields.[1]

Starting from functionalized olefins, chiral epoxides with high enantiomeric purity have been prepared by using Sharpless' ligands as efficient catalysts,[2] although satisfactory results were not obtained in the epoxidation of unfunctionalized alkenes. To reach such a goal, Katsuki[3] and Jacobsen[4] have followed a biomimetic strategy employing salen([*N*,*N*-bis(salycilidene)-ethylenediaminato])–Mn(III) derivatives as catalysts. The control of the alkene approach to the metal site bearing the transferable oxygen appears crucial in obtaining good ee values. It also seems determined by the stereochemistry of the di-imine bridge and by the presence of bulky substituents on the ligand. The real oxidant species, supposed to be an oxo Mn(V)-(salen) intermediate, is considered to have a non-planar structure. Recent theoretical studies suggest that the enantioselectivity is also related to the folding of this oxo species, which leads to the formation of a chiral pocket.[5,6]

A wide variety of structural modifications of Jacobsen's catalyst have been reported, mainly focused on the introduction of different substituents and/or additional chirality in the 3,3′-positions,[7] the use of diimine backbones derived from other diamine sources[8] and the synthesis of 'unsymmetrical' Mn(salen) complexes with two different salicylaldehyde-derived moieties.[9]

Chiral ferrocenes have been widely employed as ligands in several asymmetric reactions[10] due to their peculiar electronic and steric properties and the availability of stereoselective protocols for their synthesis.[11] Condensation of 1,1′-diaminoferrocene with salicylaldehydes gave achiral derivatives whose Mg, Ti and Zr-complexes have been structurally characterized[12] and more recently the synthesis, but not their use as catalysts, of some planar chiral ferrocene salen-type ligands has been reported.[13]

Our interest in the development of new ligands for the Mn-catalyzed enantioselective epoxidation of olefins[14] prompted us to plan the synthesis of two novel ferrocenyl derivatives **L1** and **L2**, possessing central chirality, C_2-symmetry and the structural features of the 'salen-type' ligands, in order to test their catalytic activity in this reaction and here we report the obtained results (Fig. 1).

2. Results and discussion

An examination of the possible C_2-symmetric ferrocenic scaffolds led us to identify 1,*n*-diferrocenylalkanes or 1,1′-disubstituted ferrocenes as possible starting materials; in both cases, the introduction of a stereogenic centre at the α-position with respect to the cyclopentadienyl ring seems

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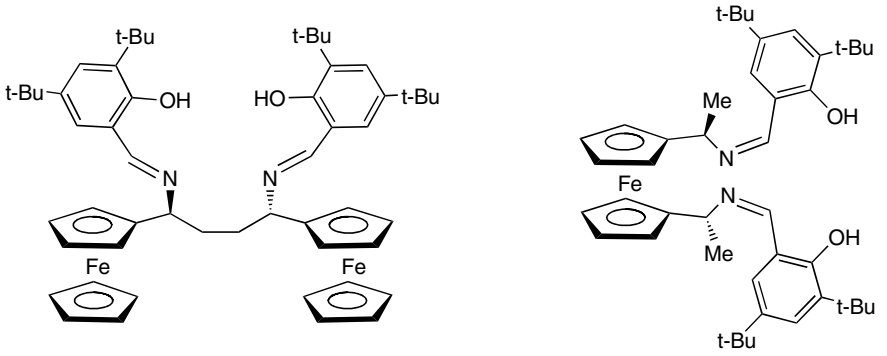


(*S*,*S*)-(+)-**L1** (*R*,*R*)-(−)-**L2**

Figure 1. Ferrocenyl–salen ligands.

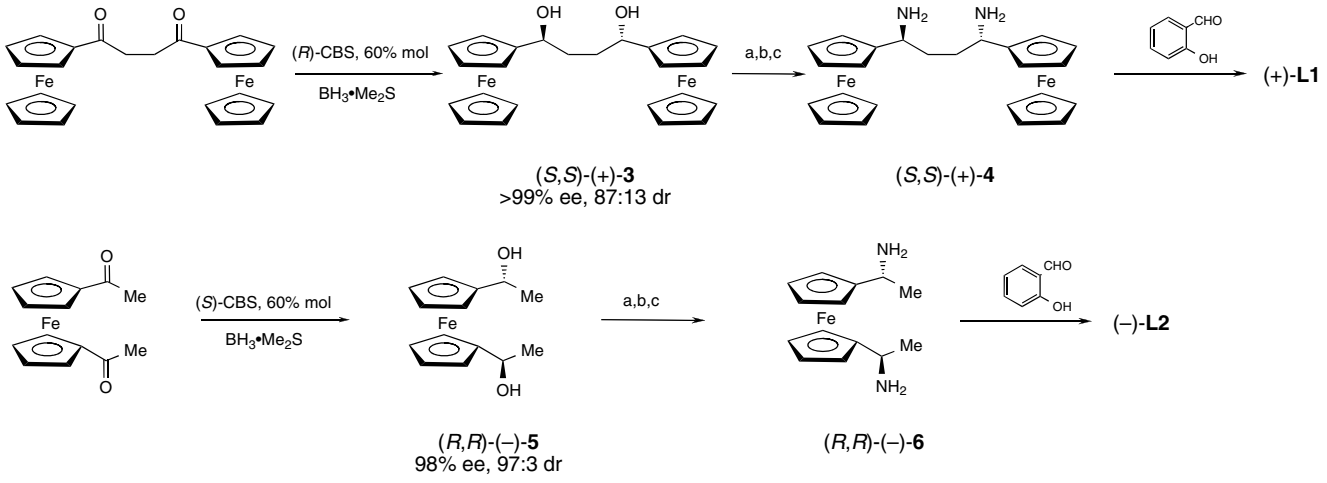
to be crucial, since these derivatives undergo nucleophilic substitution reactions with complete retention of the configuration.[15] Starting from commercially available acetylferrocenes we prepared our target ferrocenyldiamines, 1,4-diferrocenyl-1,4-diaminobutane **4** and 1,1′-(α-aminoethyl)ferrocene **5** according to Scheme 1.

Stereoselective reduction of the carbonyl groups of 1,4-diferrocenyl-1,4-butanedione, easily accessible by oxidative coupling of acetylferrocene, and 1,1′-acetylferrocene was accomplished by CBS-oxazaborolidine catalyzed reaction using $BH_3{\cdot}Me_2S$ as a hydride source.[16] Accordingly to the literature data, both diols (+)-**3**[17a] and (−)-**5**[17b] were obtained in enantiopure forms and satisfactory diastereoisomeric ratios, as determined by chiral HPLC analyses. Since attempts to perform the direct introduction of amine functions by treatment of acetylated (+)-**3** with aqueous NH_3 resulted in the formation of 2,4-diferrocenylpyrrolidine,[17a] diols (+)-**3** and (−)-**5** were converted into the corresponding diacetates and treated with NaN_3 to give homochiral diazides in nearly quantitative yields.

Diamines (+)-**4** and (−)-**6**, obtained by the reduction of the corresponding diazides, were then reacted with 2,5-di-*tert*-butyl-salicylaldehyde in refluxing ethanol to afford the 'salen–Fc'-ligands (*S*,*S*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicydene)-1,4-diferrocenyl-1,4-butanediamine, (+)-**L1** and *N*,*N*′-bis(3,5-di-*tert*-butylsalicydene)-1,1′-(α-aminoethyl)ferrocene, (−)-**L2**, whose structure was confirmed on the basis of their NMR and ESI-MS data.[18]

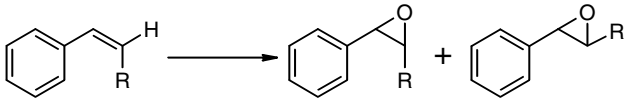
The treatment of (+)-**L1** or (−)-**L2** with $Mn(OAc)_3$ in EtOH[19] gave in nearly quantitative yield the corresponding Mn(III)-complexes, whose structure was supported on the basis of their ESI-MS spectra. The complexes obtained were used as catalysts for the epoxidation of styrene, 1,2-dihydronaphthalene and some standard *cis*-β-alkylstyrenes in CH_2Cl_2/H_2O at 25 °C using NaClO as an oxygen donor and 4-phenylpyridine N-oxide (4-PPNO) as a coligand.[20]

From the data reported in Table 1, it seems evident that both **L1**- and **L2**–Mn(III) complexes catalyzed the formation of epoxides from *cis*-alkenes in quite low yield and enantioselectivity. Despite their steric hindrance, the ferrocene units seemed too distant from the catalyst active centre to exert some control on the trajectory of the approaching alkene, thus explaining the observed lack of



Scheme 1. Synthesis of salen-type ferrocenyl ligands. Reagents and condition: (a) Ac_2O/Py; (b) NaN_3/MeOH; (c) H_2 (1.5 atm), Pd/C.

Table 1. Asymmetric epoxidation of olefins[a]



Entry	Ligand	Alkene	Conv.[b] (%)	*trans*/*cis*-epoxide ratio[b]	ee_{trans}[b] (%)	ee_{cis}[b] (%)	Abs config. *cis*-epoxide
1	**L1**	Styrene	10	—	—	9	(*R*)[c]
2	**L2**	Styrene	15	—	—	6	(*R*)[c]
3	**L1**	*cis*-β-Methylstyrene	15	12	5	40	(1*R*,2*S*)[c]
4	**L2**	*cis*-β-Methylstyrene	20	2	4	15	(1*R*,2*S*)[c]
5	**L1**	*cis*-β-Methylstyrene[d]	10	3	3	21	(1*R*,2*S*)[c]
6	**L1**	*trans*-β-Methylstyrene	64	—[e]	4	—	nd[f]
7	**L1**	*cis*-β-Ethylstyrene	13	14	7	9	nd[f]
8	**L1**	*cis*-β-Propylstyrene	10	14	7	14	nd[f]
9	**L1**	*cis*-β-Butylstyrene	14	14	4	14	nd[f]
10	**L1**	1,2-Dihydronaphthalene	42	—	—	23	(1*R*,2*S*)[c]

[a] In all experiments [Alkenes] = 0.14 M, [Catalyst] = 0.007 M, [Coligand] = [4-PPNO] = 0.07 M, [NaClO] = 0.14 M, $[Na_2HPO_4]$ = 0.05 M at pH 11.2 as buffer; in all the experiments the epoxide yields are quantitative and taken after 24 h.
[b] Determined by chiral GC.
[c] Assigned by comparison with the literature data for specific rotation.
[d] No coligand added.
[e] Exclusively *trans*-epoxide was detected.
[f] Not determined.

selectivity. In the series of *cis*-β-alkylstyrenes, comparable results were observed independent of the length of the alkyl chain, except for the methyl derivative, which gave the corresponding epoxide with the higher ee (Table 1, entry 3). The observed effect of the coligand (compare entries 3 and 5) and the absolute configuration of the *cis*-epoxides were in agreement with the literature data.[14] Unexpectedly, the reactions of *cis*-β-alkylstyrenes afforded *trans*-epoxides as the main products together with minor amounts of the *cis*-diastereomers. The only report of such selectivity refers to reactions carried out in the presence of cinchona alkaloid quaternary ammonium salts as additive.[21]

Interestingly, a better conversion of the substrate was observed starting from *trans*-β-methylstyrene, but without enantiodiscrimination (Table 1, entry 6). This is the first example of such a high reactivity with a *trans*-alkene substrate.

According to the mechanism proposed by Jacobsen,[4d,22] the epoxidation could proceed via the formation of a radical intermediate, which can collapse or undergo rotation followed by collapse. In this context, the remarkable inversion in the *trans*/*cis*-epoxide ratio observed here can be the consequence of an increased lifetime of the radical intermediate. As a speculative explanation, this radical stabilization could be due to a field effect (through space charge–dipole or dipole–dipole interactions)[23] exerted by the electron rich ferrocenyl unit in the catalyst.

In order to increase the enantioselectivity of the *trans*-epoxide, we decided to design the synthesis of new ligands containing ferrocenic units as substituents on the aldehydic moiety or directly linked with a 1,2-diiminic bridge so that a molecular recognition of alkenes could be obtained through an electronic effect, creating a preferential path to the catalyst active site.

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18. *Data for* (+)-**L1**: $[\alpha]_D = +129.2$ (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 400.1 MHz): δ 1.31 (18H, s, CH_3–), 1.48 (18H, s, CH_3–), 1.86 (4H, m, CH_2–), 4.02 (2H, m, CH–N), 4.07 (10H, s, Cp′), 4.10 (2H, br s, Cp), 4.13 (2H, br s, Cp), 4.15 (2H, br s, Cp), 4.24 (2H, br s, Cp), 7.15 (2H, br s, Ar–H), 7.40 (2H, br s, Ar–H), 8.39 (2H, s, CH=N), 13.98 (2H, br s, –OH); ^{13}C NMR ($CDCl_3$, 100.03 MHz): δ 29.49 (CH_3), 31.51 (CH_3), 34.13 (C–), 34.82 (C–), 35.07 (CH_2), 66.42 (CH), 66.87 (CH), 67.24 (CH), 67.75 (CH), 68.34 (CH), 68.60 (CH), 91.50 (C–), 117.63 (C–), 125.92 (CH), 126.97 (CH), 136.72 (C–), 139.98 (C–), 158.20 (C–), 164.31 (C=N); ESI-MS: *m*/*z*: 889.7 $[M{\cdot}H]^+$. Anal. Calcd for $C_{54}H_{68}Fe_2N_2O_2$ (888.24): C, 72.95; H, 7.72; N, 3.15. Found: C, 72.75; H, 7.69; N, 3.12.
Data for (−)-**L2**: $[\alpha]_D = -164.8$ (*c* 0.2, $CHCl_3$); ^1H NMR (CD_3OD, 400.1 MHz): δ 1.31 (18H, s, CH_3–), 1.45 (18H, s, CH_3–), 1.53 (6H, d, $J = 6.5$ Hz, –CH_3), 4.13 (2H, br s, Cp), 4.16 (2H, br s, Cp), 4.18 (4H, br s, Cp), 4.28 (2H, q, $J = 6.5$ Hz, CH–N), 7.14 (2H, d, $J = 1.8$ Hz, Ar–H), 7.40 (2H, d, $J = 1.8$ Hz, Ar–H), 8.40 (2H, s, CH=N), ^{13}C NMR ($CDCl_3$, 100.03 MHz, 330 K): δ 23.69 (CH_3), 29.63 (CH_3), 31.59 (CH_3), 34.21 (C–), 34.16 (C–), 62.78 (CH), 67.13 (CH), 67.28 (CH), 68.53 (CH), 68.67 (CH), 92.89 (C–), 118.07 (C–), 125.86 (CH), 126.92 (CH), 137.00 (C–), 139.98 (C–), 158.40 (C–), 164.87 (C=N); ESI-MS: *m*/*z*: 705.6 $[M{\cdot}H]^+$. Anal. Calcd for $C_{44}H_{60}FeN_2O_2$ (704.33): C, 74.96; H, 8.59; N, 3.98. Found: C, 74.78; H, 8.53; N, 3.94.
19. To a solution of ligand (+)-**L1** or (−)-**L2** (0.05 mmol) in abs EtOH (15 mL) a solution of $Mn(OAc)_3{\cdot}2H_2O$ (0.075 mmol) in abs EtOH (5 mL) was added. The dark solution was allowed to stir overnight at room temperature and the reaction monitored by TLC. Evaporation of the solvent gave a residue, which was dissolved in CH_2Cl_2, filtered and concentrated to produce the Mn(III)-complex in a nearly quantitative yield. ESI-MS: *m*/*z*: 942.2 $[M]^+$ for **L1**–Mn(III) complex and *m*/*z*: 757.6 $[M]^+$ for **L2**–Mn(III) complex.
20. *General procedure for the catalyzed epoxidation of alkenes:* To a stirred solution of alkene (0.35 mmol) in CH_2Cl_2 (2.5 mL), catalyst (0.0175 mmol), 4-PPNO (0.175 mmol) and buffered bleach (0.35 mmol, buffered to pH 11.2 with 0.05 M Na_2HPO_4) were added. The reaction was kept at 25 °C and monitored by GC on a DMePeBETACDX (styrene and 1,2-dihydronaphthalene) or DMeTButilsililBETA columns (both 25 m × 0.25 mm ID, 0.25 μm film) against an internal quantitative standard (*n*-decane or *n*-nonane).
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