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Synthesis of ferrocenyl-oxazolines by ring expansion of *N*-ferrocenoyl-aziridine-2-carboxylic esters

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Abstract—A synthesis of ferrocenyl-oxazolines is described using an iodide-mediated ring expansion of *N*-ferrocenoyl-aziridine-2-carboxylic esters. The ring enlargements take place with full stereocontrol, namely net retention of configuration. Modification of the ester function by a Grignard reaction leads to three new types of ferrocenyl-oxazoline carbinol ligands, which were used as chiral ligands in the asymmetric addition of diethylzinc to benzaldehyde (e.e.s ranging from 46 to 62%). The planar chiral ferrocenyl-oxazoline carbinol ligand gave a very good result (e.e. 90%) in the palladium-catalyzed allylic substitution of 1,3-diphenyl prop-2-enylacetate with dimethyl malonate.

1. Introduction

Chiral nonracemic oxazolines have found widespread application as ligands in a multitude of metal-catalyzed asymmetric reactions.[1] Among these ligands the ferrocenyl-oxazolines (Fig. 1) constitute a special group as they possess both central and planar chirality. These oxazolines have been described independently by several groups[2] and various types of effective planar chiral ferrocene ligands have been developed. These chiral ligands have been extensively and successfully applied in palladium catalyzed allylic substitutions[2a,c,e,f,i,3] and in asymmetric alkylations of aldehydes with dialkylzinc.[2b,d,4]

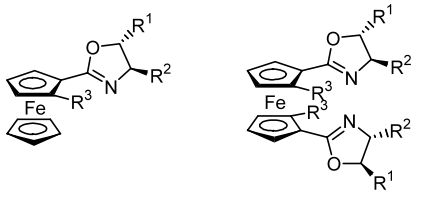

Figure 1. Ferrocenyl-oxazolines.

An important issue in ligand design is the installation of a substituent that can be readily modified in order to access a series of structurally closely related ligands. A carboxylic ester function is particularly suitable for this purpose. Herein we report a preparation of mono, planar chiral and bis-ferrocenyl-oxazolines by ring expansion of *N*-ferrocenoyl-aziridine-2-carboxylic esters and some applications of these novel chiral oxazolines in asymmetric synthesis.

Aziridines belong to the class of three-membered ring heterocycles that has attracted the interest of many chemists for more than a century.[5] Primarily due to their intrinsically high reactivity they are very versatile species for synthetic elaboration.[6] The presence of an additional functional group is especially valuable; for instance, aziridine-2-carboxylic acids[7] can be considered as α- as well as β-amino acids. Ring expansion of aziridines is an attractive method for the preparation of a wide variety of five-membered ring aza-heterocycles.[7] The majority of these ring enlargements proceed with full stereochemical control.[7–9] The modified Ritter reaction[7] of aziridinecarboxylic esters, i.e. treatment with a nitrile in the presence of a Lewis catalyst, leads to imidazolines[7c,10] or oxazolines[7c,11] depending on the substituent on the nitrogen atom. Ring expansion of *N*-acyl-aziridines can also be accomplished under thermal conditions to give oxazolines.[7c,12] Only one example has been reported so far in the literature describing

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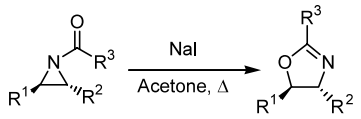
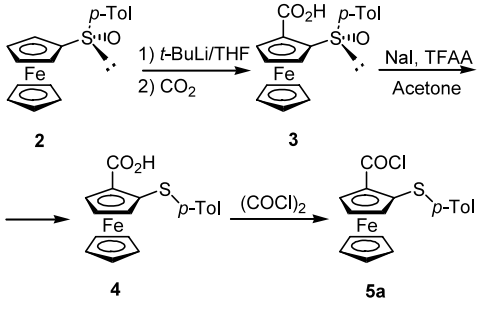
the synthesis of ferrocenyl-oxazolines from the reaction of ferrocenecarbonyl chloride with aziridenes and subsequent acid-catalyzed isomerization.[13] Herein the focus is on the use of the so called Heine reaction [14] involving the treatment of *N*-acyl-aziridines with sodium iodide in acetone (Scheme 1). In the initial step ring opening takes place by iodide ion. Subsequent ring closure by S_N2 displacement of iodide by reaction with the negative oxygen centre then gives the oxazolines. This process proceeds with double inversion at the same carbon atom, thus with net retention of configuration.[7c,14]



Scheme 1. Heine reaction: iodide-mediated ring expansion.

2. Results and discussion

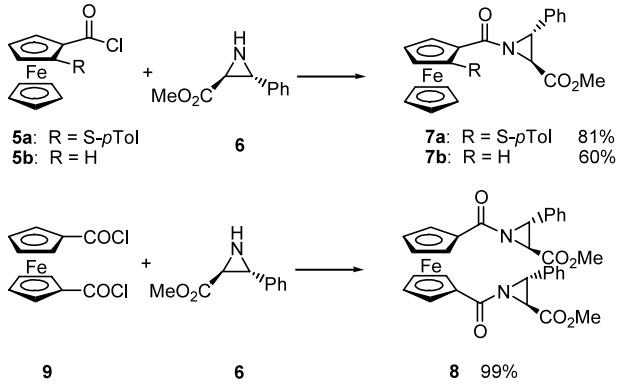
Two essential building blocks are needed for the preparation of the non-racemic target ferrocenyl-oxazoline **1a**, viz. a ferrocenecarboxylic acid derivative and a suitable aziridine-2-carboxylic ester, both of high enantiopurity. The first of these building blocks was prepared, as previously described by us,[15] from (*S*)-ferrocenyl *p*-tolyl sulfoxide **2**,[16] by diastereoselective *ortho*-lithiation followed by electrophilic quenching with CO_2 and deoxygenation of the obtained (S_{Fc},S_S)-2-(*p*-tolylsulfinyl)-ferrocenecarboxylic acid **3**, as depicted in Scheme 2. The yield of the deoxygenation step has been improved considerably by the use of sodium iodide and trifluoroacetic anhydride in acetone at 0°C[17] instead of Lawesson's reagent that we used earlier.[15] Enantiopure (S_{Fc})-2-(*p*-tolylsulfanyl)-ferrocenecarboxylic acid **4** was obtained in 94% yield. This acid was converted into the acid chloride **5a** by treatment with oxalyl chloride.



Scheme 2.

The chosen aziridinecarboxylic ester, viz. methyl (2*S*,3*R*)-3-phenyl-aziridine-2-carboxylate **6**, was prepared from the corresponding oxirane ester as described previously.[18]

The preparation of the *N*-ferrocenoyl-aziridine **7a** was achieved by the coupling of (S_{Fc})-2-(*p*-tolylsulfanyl)-ferrocenecarbonyl chloride **5a** with a stoichiometric amount of **6** in the presence of triethylamine. Product **7a** was obtained in 81% yield (Scheme 3).

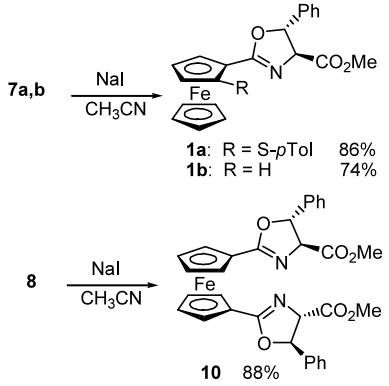


Scheme 3. Synthesis of *N*-ferrocenoyl-aziridines.

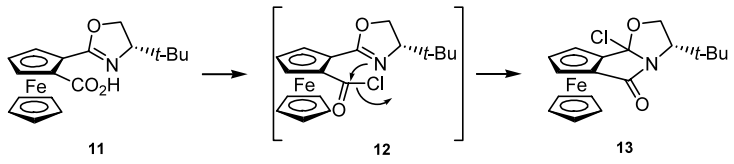
In a similar manner ferrocenecarbonyl chloride **5b**[15] was coupled with the aziridine **6** to give the ferrocenoyl-aziridine ester **7b** in 60% yield (Scheme 3).

A ferrocene derivative containing two aziridine units, namely **8**, was obtained similarly in quantitative yield, by coupling of ferrocene-1,1′-dicarbonyl dichloride **9**[15] with two equivalents of the aziridine ester **6** (Scheme 3).

In the latter two ferrocenoyl-aziridines the chirality only resides in the three-membered ring. The ring expansion of products **7a**, **7b** and **8** was performed in boiling acetonitrile in the presence of a catalytic amount of sodium iodide affording the ferrocenyl-oxazoline-carboxylates **1a**, **1b** and **10** in 86, 74 and 88% yield, respectively (Scheme 4). All three compounds have the phenyl and ester substituent in a *trans* configuration as was deduced from the coupling constants of the oxazoline ring protons in the ^1H NMR spectra.[19] Moreover, the ^1H and ^{13}C NMR spectra of the crude **1a** possessing planar chirality, showed only one set of signals, thus ruling out the presence of a second diastereomer that could have been formed by a partial racemization during the ring enlargement.



Scheme 4. Synthesis of ferrocenyl-oxazolines.

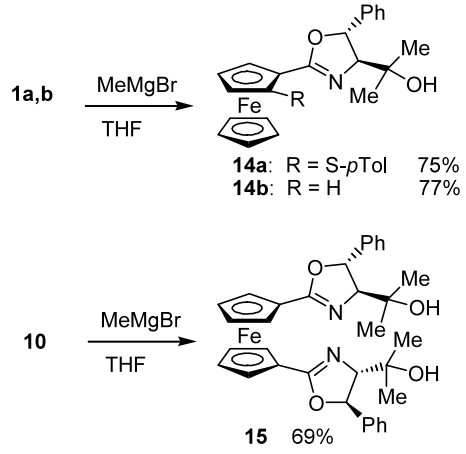


Scheme 5.

The observation that *trans* oxazolines are obtained from the *trans* relative aziridine ester is in full accordance with the mechanistic course of the ring expansion reaction, i.e. a double inversion process resulting in net retention (cf. Scheme 1).[7c,14]

We also investigated the preparation of a planar chiral 1,2-bis-oxazoline starting from (4*S*)-*t*-butyl-2-oxazolin-2-yl-ferrocene-(2*S*)-carboxylic acid **11**.[20] Surprisingly, during the attempted transformation of the acid **11** into the corresponding acid chloride **12** under various reaction conditions, namely oxalyl chloride and oxalyl chloride in the presence of Et_3N or PPh_4 in CCl_4, an unexpected tricyclic product **13** was obtained in quantitative yield. The structure of **13** was assigned on the basis of spectroscopic and analytical data (see experimental). A possible explanation for the formation of **13** is depicted in Scheme 5.

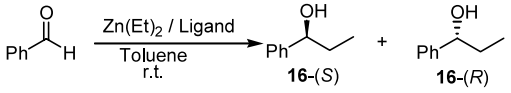
The new ferrocenyl-oxazolines **1a**,**b** and ferrocenyl-bisoxazoline **10** have been modified by a Grignard reaction of the ester function as shown in Scheme 6. Reaction of **1a**,**b** and **10** with methylmagnesium chloride in THF at room temperature gave the oxazoline carbinols **14a**,**b** and **15**, respectively, in high yields. These oxazoline carbinols are a new type of β-imino alcohols that may serve as ligands in asymmetric synthesis.[21]



Scheme 6. Synthesis of ferrocenyl oxazoline carbinols.

The newly prepared chiral ligands **14a**,**b** and **15** were tested in the Zn(II)-catalysed asymmetric alkylation of benzaldehyde with diethylzinc. The results are collected in Table 1. These results reveal that the C_2-symmetric bisoxazoline **15** (Table 1, entry 3) performs better in terms of yield and enantiomeric excess than the monosubstituted oxazoline **14b** and the chiral planar oxazoline **14a**.

Table 1. Zn(II)-catalyzed asymmetric alkylation of benzaldehyde with diethylzinc[a]



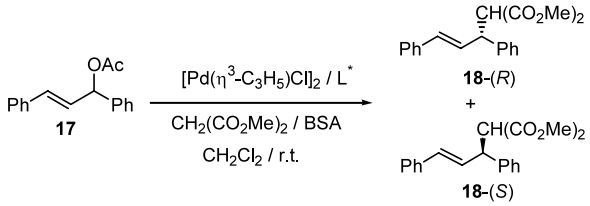
Entry	Ligand	Yield of **16** (%)[b]	E.e. of **16** (%)[c]	Abs. conf.[d]
1	**14a**	76	46	*R*
2	**14b**	60	46	*R*
3	**15**	80	62	*R*

[a] Conducted with ligand (0.05 mmol), benzaldehyde (1 mmol) and diethylzinc (1.5 mmol) in toluene (5 mL) for 24 h at rt.
[b] Isolated yield.
[c] Determined by chiral GC.
[d] Determined by comparing the sign of specific rotation of **16** with a commercially available sample.

We also compared the catalytic activity of the planar chiral ferrocenyl-oxazoline-carbinol **14a** with the oxazoline containing the unmodified ester function **1a** in palladium-catalyzed allylic substitution of 1,3-diphenyl-prop-2-enyl acetate **17** with the nucleophile derived from dimethyl malonate. The obtained results are collected in Table 2. The alkylation reactions proceed at room temperature, and after a reaction time of 3 and 2 h for **1a** and **14a**, respectively, **18** was isolated in quantitative yield and with an e.e. of 68 and 90%.

In summary, the synthesis of three new types of ferrocenyloxazolines has been accomplished successfully by employing a stereocontrolled ring expansion of the corresponding ferrocenoyl-aziridine derivatives. The presence of an ester function in these ligands in the α position with respect to the imino group allowed the synthetic modification to three new ferrocenyl-oxazoline carbinol ligands. The performance of these ferrocenyl ligands in asymmetric catalysis is moderate for the diethylzinc addition to benzaldehyde and acceptable to good for the palladium mediated allylic substitution. These results are not as good as expected in view of the excellent reputation of oxazolines in this respect. It is again demonstrated that the efficiency of chiral ligands cannot be predicted beforehand.

Table 2. Palladium-catalyzed allylic substitution reaction[a]



Entry	Ligand	Time (h)[b]	Yield of **18** (%)[c]	E.e. of **18** (%)[d]	Abs. conf.[e]
1	**1a**	3	99	68	*R*
2	**14a**	2	97	90	*R*

[a] **17** 1.0 mmol, $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ 0.025 mmol, ligand 0.1 mmol, $CH_2(CO_2Me)_2$ 3 mmol, BSA 3 mmol, KOAc 0.03 mmol, CH_2Cl_2 3 mL.
[b] When TLC monitoring indicated complete consumption of the allylacetate.
[c] Isolated yield.
[d] Determined by chiral HPLC.
[e] The absolute configuration of **18** was assigned through comparison of the sign of the specific rotation with the literature data.[22]

3. Experimental

3.1. General

Melting points (uncorrected) were determined with a Büchi melting point apparatus. ^1H and ^{13}C NMR spectra were recorded with a Varian Gemini 300 at 300 and 75.46 MHz, respectively, using $CDCl_3$ solutions of the samples. Chemical shifts (δ) are reported in ppm relative to $CHCl_3$ ($\delta = 7.26$ for ^1H and $\delta = 77.0$ for ^{13}C). *J* values are given in Hz. ^{13}C NMR spectral assignments were made by DEPT experiments. IR spectra were recorded on a Perkin–Elmer model 257 grating spectrometer. Mass spectra were obtained using a VG 7070-E spectrometer at an ionizing voltage of 70 eV or with an electrospray ionization source (ESIMS). All the ESIMS spectra were performed using MeOH as the solvent optical rotations were measured with Perkin Elmer Polarimeter 341 and specific rotations are given in 10^{-1} deg cm^2 g^{-1}. The originality of all compounds was checked by a CAS-on-line structure search. Reactions were conducted in oven-dried (120°C) glassware under a positive Ar atmosphere. Transfer of anhydrous solvents or mixtures was accomplished with oven-dried syringes/septum techniques. THF was distilled from sodium/benzophenone prior to use and stored under Ar. CH_2Cl_2 was passed through basic alumina and distilled from CaH_2 prior to use. Other solvents were purified by standard procedures. Light petroleum ether refers to the fraction with a bp 40–60°C. The reactions were monitored by TLC, using silica gel plates (Baker-flex IB2-F). Column chromatography was performed with Merck silica gel 60 (70–230 mesh). Preparative thick layer chromatography was carried out on glass plates using a 1 mm layer of Merck silica gel 60 Pf 254. Methyl (2*S*,3*R*)-3-phenyl-aziridine-2-carboxylate **6** was prepared following a literature procedure.[18] All chemicals were used as obtained or purified by distillation as needed.

3.2. Improved procedure for the deoxygenation of ($S_{Fc}S_S$)-2-(*p*-tolylsulfinyl)-ferrocenecarboxylic acid 3 to (S_{Fc})-2-(*p*-tolylsulfanyl)-ferrocenecarboxylic acid 4

To a stirred solution of **3** (250 mg, 0.68 mmol) and NaI (250 mg, 1.70 mmol) in acetone (2.5 mL) at 0°C, a solution of trifluoroacetic anhydride (0.2 ml, 2.7 mmol) in acetone (2.5 mL) was slowly added. After stirring for 30 min at 0°C, the reaction mixture was concentrated in vacuo and water (8 mL) was added. The mixture was extracted with $CHCl_3$ (3×5 mL) and the organic layer was washed with a 10% solution of $Na_2S_2O_3$, dried and concentrated. The residue was purified by chromatography on silica gel (light petroleum/EtOAc, 2:3) giving (S_{Fc})-2-(*p*-tolylsulfanyl)-ferrocenecarboxylic acid **4**[15] as a red solid (220 mg, 92%).

3.3. General procedure for the synthesis of *N*-ferrocenoylaziridines 7a,b and 8

Triethylamine and a solution of the appropriate acid chloride in dry CH_2Cl_2 were added to a solution of methyl (2*S*,3*R*)-3-phenyl-aziridine-2-carboxylate **6** in dry CH_2Cl_2 (15 mL). The resulting solution was stirred at room temperature until disappearance of the starting aziridine (TLC: hexane/EtOAc, 1:1) and then concentrated in vacuo. The residue was dissolved in $CHCl_3$ (20 mL) and poured into water. The organic layer was separated, washed with water and dried (Na_2SO_4). The crude product was then purified by column chromatography (hexane/EtOAc, 1:1) affording the title compounds as red-orange solids.

3.3.1. Methyl (2*S*,3*R*)-1-[(S_{Fc})-(*p*-tolylsulfanyl)ferrocenoyl]-3-phenyl-aziridine-2-carboxylate 7a. Starting from **5a** (1.0 g, 2.7 mmol), triethylamine (0.45 mL, 3.2 mmol) and **6** (0.28 g, 1.6 mmol), **7a** was obtained as a red-orange solid (0.84 g, 61%); mp 121–122°C; $[\alpha]_D^{20}$ −32.6

(c 0.59 $CHCl_3$); (Found: C, 65.61; H, 4.98. $C_{28}H_{25}FeNO_3S$ requires C, 65.76; H, 4.93); ν_{max} (CCl_4)/cm^{-1} 1745 (CO) and 1677 (CON); δ_H (300 MHz, $CDCl_3$) 2.30 (3H, s, CH_3), 3.21 (1H, d, J 2.4, CH), 3.51 (3H, s, CH_3), 3.96 (1H, d, J 2.4, CH), 4.29 (5H, s, FcH), 4.41 (1H, dd, J_1,J_2 2.7, FcH), 4.44 (1H, dd, J 2.7 and 1.7, FcH), 4.83 (1H, dd, J 2.7 and 1.7, FcH), 7.06 (2H, d, J 8.3, ArH), 7.11 (2H, d, J 8.3, ArH), 7.28–7.43 (5H, m, ArH); δ_C (300 MHz, $CDCl_3$) 21.0 (q), 45.7, 45.85 (d), 52.2 (q), 71.2, 71.65, 72.15, 127.0, 128.4, 128.8, 129.5 (d), 135.8 (s); m/z (EI) 511 (M^+), 335, 185, 121, 56 beside 2-[(S_{Fc})-(p-tolylsulfanyl)]ferrocen anhydride (130 mg, 20%) mp 135–137°C; $[\alpha]_D^{20}$ −98.8 (c 0.432, $CHCl_3$); (Found: C, 62.88; H, 4.45. $C_{36}H_{30}Fe_2O_3S_2$ requires C, 62.99; H, 4.41); ν_{max} (CCl_4)/cm^{-1} 1773, 1721 (CO); δ_H (300 MHz, $CDCl_3$) 2.30 (3H, s, CH_3), 4.40 (5H, s, FcH), 4.52 (2H, m, FcH), 4.98 (1H, m, CH), 7.10 (2H, d, J 8.3, ArH), 7.21 (2H, d, J 8.3, ArH); δ_C (75 MHz, $CDCl_3$) 21.0 (q), 69.2 (s), 71.6, 71.9, 72.8, 77.6 (d), 85.2 (s), 129.6, 130.0 (d), 133.6, 136.6, 166.7 (s); m/z (ESI) 709 (M^++Na).

3.3.2. Methyl (2*S*,3*R*)-1-ferrocenoyl-3-phenyl-aziridine-2-carboxylate 7b. Starting from ferrocenoyl chloride **5b** (1.0 g, 4.3 mmol), triethylamine (1.2 mL, 8.6 mmol) and **6** (0.76 g, 4.3 mmol), **7b** was obtained as a red-orange solid (1.0 g, 60%); mp 150–151°C; $[\alpha]_D^{20}$ −33.2 (c 0.48, $CHCl_3$); (Found: C, 64.57; H, 4.99. $C_{21}H_{19}FeNO_3$ requires C, 64.80; H, 4.92); ν_{max} (CCl_4)/cm^{-1} 1737 (CO) and 1664 (CON); δ_H (300 MHz, $CDCl_3$) 3.15 (1H, d, J 2.2,CH) 3.80 (3H, s, CH_3), 4.10 (1H, d, J 2.2, CH), 4.30 (5H, s, FcH), 4.38 (1H, m, FcH), 4.42 (1H, m, FcH),), 4.60 (1H, m, FcH), 4.75 (1H, m, FcH), 7.45 (5H, br s, ArH); δ_C (300 MHz, $CDCl_3$) 43.5, 46.45 (d), 52.8 (q), 69.5, 70.0, 71.5 (d), 74.0 (s), 126.2, 128.7, 129.0 (d), 135.3, 167.5, 178.7 (s); m/z (ESI) 390 (M^++1), 412 (M^++Na).

3.3.3. 1,1′-Bis[(3*R*,2*S*)keto(3-phenyl-2-methoxycarbonyl)-aziridin-1-yl]ferrocene 8. Starting from 1,1′-bis-(chlorocarbonyl)ferrocene **9** (1.0 g, 3.22 mmol), triethylamine (2.1 mL, 14.9 mmol) and **6** (1.3 g, 7.46 mmol), **8** was obtained as a red-orange solid (1.9 g, 99%); mp 130–131°C; $[\alpha]_D^{20}$ +115.2 (c 0.73, $CHCl_3$); (Found: C, 64.78; H, 4.91. $C_{32}H_{29}FeN_2O_6$ requires C, 64.88; H, 4.76); ν_{max} (CCl_4)/cm^{-1} 1744 (CO) and 1644 (CON); δ_H (300 MHz, $CDCl_3$) 3.18 (1H, d, J 2.0, CH), 3.79 (3H, s, CH_3), 4.11 (1H, d, J 2.0, CH), 4.55 (2H, m, FcH), 4.77 (1H, m, FcH), 4.81 (1H, m, FcH), 7.30–7.42 (5H, m, ArH); δ_C (300 MHz, $CDCl_3$) 43.5 (q), 46.2, 52.7, 70.6, 71.3, 73.6, 73.8 (d), 75.6 (s) 126.3, 128.7, 128.9 (d), 134.9, 167.3, 177.5 (s); m/z (EI) 592 (M^+), 560, 528, 91, 65, 56.

3.4. General procedure for the synthesis of ferrocenyl-oxazolines 1a,b and 10

NaI (0.3 mmol) was added to a solution of the appropriate N-ferrocenoyl aziridine (2.0 mmol) in dry CH_3CN (80 mL). The mixture was heated at reflux until disappearance of the starting product (TLC, hexane/EtOAc, 1:1) and then concentrated in vacuo. The residue was dissolved in $CHCl_3$ (25 mL) and poured into water (25 mL). The organic layer was separated, washed with water and with a 10% solution of $Na_2S_2O_3$, and then dried (Na_2SO_4). The crude product was purified by column chromatography (hexane/EtOAc, 1:1) affording the title compounds as red-orange solids.

3.4.1. Methyl (5*R*,4*S*)-2-[(S_{Fc})-(p-tolylsulfanyl)ferrocenyl]-5-phenyl-oxazoline-4-carboxylate 1a. Starting from **7a** (1.0 g, 1.9 mmol), **1a** was obtained as a red/orange solid (690 mg, 68%); mp 71–72°C; $[\alpha]_D^{20}$ +230 (c 0.815, $CHCl_3$); (Found: C, 65.59; H, 4.86. $C_{28}H_{25}FeNO_3S$ requires C, 65.76; H, 4.93); ν_{max} (CCl_4)/cm^{-1} 1745 (CO) and 1637 (OCN); δ_H (300 MHz, $CDCl_3$) 2.30 (3H, s, CH_3), 3.81 (3H, s, OCH_3), 4.35 (5H, s, FcH), 4.51 (2H, m, FcH), 4.62 (1H, d, J 6.3, CH), 5.08 (1H, m, FcH), 5.81 (1H, d, J 6.3, CH), 7.00 (2H, d, J 8.3, ArH), 7.08 (2H, d, J 8.3, ArH), 7.12–7.32 (9H, m, ArH); δ_C (75 MHz, $CDCl_3$) 20.9, 52.6 (q), 70.9, 71.5, 72.1, 76.3, 77.5, 82.7, 125.0, 128.1, 128.2, 128.6, 129.4 (d), 135.4, 139.8, 168.0, 171.65 (s); m/z (ESI) 512 (M^++1), 534 (M^++Na).

3.4.2. Methyl (5*R*,4*S*)-2-ferrocenyl-5-phenyl-oxazoline-4-carboxylate 1b. Starting from **7b** (0.8 g, 3.2 mmol), **1b** was obtained as a red-orange solid (0.92 g 74%); mp 55–57°C; $[\alpha]_D^{20}$ +51.5 (c 0.71, $CHCl_3$); (Found: C, 64.58; H, 4.83. $C_{21}H_{19}FeNO_3$ requires C, 64.80; H, 4.92); ν_{max} (CCl_4)/cm^{-1} 1745 (CO) and 1648 (OCN); δ_H (300 MHz, $CDCl_3$) 3.85 (3H, s, CH_3), 4.25 (5H, s, FcH), 4.40 (2H, m, FcH), 4.67 (1H, d, J 6.9, CH), 4.90 (2H, m, FcH), 5.75 (1H, d, J 6.9, CH), 7.30–7.45 (5H, m, ArH); δ_C (75 MHz, $CDCl_3$) 52.7 (q), 69.3, 69.4, 69.8, 70.7, 70.8, 76.6, 82.65, 125.5, 128.6, 128.9 (d), 139.7, 168.8, 171.6 (s); m/z (EI) 389 (M^+), 213, 185, 56.

3.4.3. 1,1′-Bis[(5*R*,4*S*)-5-phenyl-4-methoxycarbonyl-oxazolin-2-yl]ferrocene 10. Starting from **8** (1.2 g, 3.9 mmol), **10** was obtained as a red solid in 78% yield (2.0 g, 88%); mp 64–66°C (Et_2O); $[\alpha]_D^{20}$ +128.3 (c 0.5, $CHCl_3$); (Found: C, 64.94; H, 4.81. $C_{32}H_{28}FeN_2O_6$ requires C, 64.88; H, 4.76); ν_{max} (CCl_4)/cm^{-1} 1745 (CO) and 1649 (OCN); δ_H (300 MHz, $CDCl_3$) 3.82 (3H, s, CH_3), 4.45 (1H, m, FcH), 4.51 (1H, m, FcH), 4.67 (1H, d, J 7.1, CH), 4.93 (1H, m, FcH), 4.96 (1H, m, FcH), 5.77 (1H, d, J 7.1, CH), 7.31–7.41 (5H, m, ArH); δ_C (75 MHz, $CDCl_3$) 52.8 (q). 70.7, 71.2, 72.8, 73.0, 76.7, 83.0, 125.7 128.7, 128.9, (d) 139.4, 167.8, 171.4 (s); m/z (EI) 592 (M^+), 560, 528, 324, 91, 56.

3.5. General procedure for the synthesis of oxazoline carbinols 14a,b and 15

MeMgBr (3 M in THF) was added to a cooled (0°C) solution of the appropriate ferrocenyloxazoline in dry THF (5 mL). The reaction mixture was left at room temperature until disappearance of the starting product (30 min to 1h, TLC, hexane/EtOAc, 2:1) and then quenched with aqueous NH_4Cl and extracted with EtOAc (2×5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography (hexane/EtOAc, 2:1) affording the title compounds as red-orange solids.

3.5.1. (5*R*,4*S*)-2-[(S_{Fc})-(*p*-Tolylsulfanyl)ferrocenyl]-5-phenyl-4-(1-hydroxy-1-methylethyl) oxazoline 14a. Starting from **1a** (500 mg, 0.98 mmol) and 0.65 mL (2.0 mmol) of MeMgBr solution, **14a** was obtained as a red/orange solid (385 mg,77%); mp 189–191°C (Et_2O); $[\alpha]_D^{20}$ +98.0 (*c* 0.585, $CHCl_3$); (Found: C, 68.27; H, 5.83. $C_{29}H_{29}FeNO_2S$ requires C, 68.10; H, 5.72); ν_{max} (CCl_4)/cm^{-1} 1656 (CN); δ_H (300 MHz; $CDCl_3$) 1.09 (3H, s, CH_3), 1.10 (3H, s, CH_3), 1.48 (1H, s, OH), 2.25 (3H, s, CH_3), 3.90 (1H, d, *J* 6.0, CH), 4.32 (5H, s, FcH), 4.47 (1H, t, *J* 2.8, FcH), 4.53 (1H, br dd, *J* 2.3, FcH), 4.94 (1H, m, FcH), 5.30 (1H, d, *J* 6.0,CH), 6.97 (4H, m, ArH), 7.26 (5H, m, ArH); δ_C (75 MHz, $CDCl_3$) 20.9, 25,0, 26.5 (q), 70.2, 71.2, 72.0, 77.4 (d), 71.45 (s), 81.1, 84.1 (s), 125.7, 126.7, 127.9, 128.6, 129.4 (d), 135.0. 136.0, 141.7 (s); *m*/*z* (ESI) 512 (M^++1), 534 (M^++Na).

3.5.2. (5*R*,4*S*)-2-Ferrocenyl-5-phenyl-4-(1-hydroxy-1-methylethyl)oxazoline 14b. Starting from **1b** (500 mg, 1.3 mmol) and 0.9 mL (2.6 mmol) of MeMgBr solution, **14b** was obtained as a orange solid (380 mg, 75%); mp 143–144°C; $[\alpha]_D^{20}$ −31.6 (*c* 0.98, $CHCl_3$); (Found: C, 67.74; H, 5.82. $C_{22}H_{23}FeNO_2$ requires C, 67.88; H, 5.96); ν_{max} (CCl_4)/cm^{-1} 3622 (OH) and 1644 (CN); δ_H (300 MHz; $CDCl_3$) 1.28 (3H, s, CH_3), 1.38 (3H, s, CH_3), 2.04 (1H, br s, OH), 4.00 (1H, d, *J* 6.6, CH), 4.24 (5H, s, FcH), 4.39 (2H, dd, *J* 1.9 and 1.9, FcH), 4.84 (2H, dd, *J* 1.9 and 1.9, FcH), 5.43 (1H, d, *J* 6.6, CH), 7.35–7.41 (5H, m, ArH); δ_C (75 MHz, $CDCl_3$) 25.5, 26.75 (q); 69.1, 69.8, 70,1 (d), 71.8 (s), 81.8, 84.7, 126.2, 128.0, 128.3 (d), 141.9 (s); *m*/*z* (ESI) 390 (M^++1), 412 (M^++Na).

3.5.3. 1,1′-Bis[(4*S*,5*R*)-(5-phenyl-4-(1-hydroxy-1-methylethyl))oxazolin-2-yl]-ferrocene 15. Starting from **10** (500 mg, 0.84 mmol) and 1.1 mL (3.4 mmol) of MeMgBr solution, **15** was obtained as a red solid (288 mg, 69%); mp 67–70°C (Et_2O); $[\alpha]_D^{20}$ −67 (*c* 0.43, $CHCl_3$); (Found: C, 68.99; H, 6.05. $C_{34}H_{36}FeN_2O_4$ requires C, 68.92; H, 6.12); ν_{max} (CCl_4)/cm^{-1} 3375 (OH) and 1654 (CN); δ_H (300 MHz; $CDCl_3$) 1.23 (3H, s, CH_3), 1.31 (3H, s, CH_3), 2.68 (1H, Br s, OH), 4.03 (1H, d, *J* 7.4, CH), 4.42 (1H, m, FcH), 4.47 (1H, m, FcH), 4.84 (1H, m, FcH), 4.87 (1H, m, FcH), 5.42 (1H, d, *J* 7.4, CH,), 7.29–7.47 (5H, m, Ph); δ_C (75 MHz; $CDCl_3$) 25.4, 27.2 (q), 71.4 (s), 71.1, 71.15, 71.5, 72.2, 82.4, 84.0, 126.7, 128.4, 128.9 (d) 141.2, 165.9 (s); *m*/*z* (EI) 592 (M^+), 356, 91, 65, 56.

3.6. Tricyclic product 13

Oxalyl chloride (0.35 mL, 3.96 mmol) was added to a stirred solution of [4(*S*)-*tert*.butyl-2-oxazolin-2-yl]-ferrocene-2(*S*)-carboxylic acid **11** (0.70 g, 1.98 mmol) in dry CH_2Cl_2 (15 mL) under an argon atmosphere at room temperature. After 15 min the excess of oxalyl chloride and the solvent were removed in vacuo and the residue was dissolved in CH_2Cl_2/EtOAc. After filtration the resulting solution was concentrated in vacuo, affording 0.72 g (98%) of compound **13** (red solid) as a mixture of two diastereoisomers: ν_{max} (CCl_4)/cm^{-1} 1757 (CO); δ_H (300 MHz; $CDCl_3$) [minor isomer in parenthesis] [0.95 (9H, s, CH_3)], 1.12 (9H, s, CH_3), [3.78 (1H, dd, J_1 7.3, J_2 2.2, CH)], 3.81 (1H, dd, J_1 7.3, J_2 2.2, CH), [4.10 (1H, dd, J_1 7.3, J_2 2.2, CH)], 4.15 (1H, dd, J_1 7.3, J_2 2.2, CH), [4.40 (5H, s, FcH)], 4.46 (5H, s, FcH), 4.80–4.70 (m); 5.20–4.96 (m); δ_C (75 MHz; $CDCl_3$) [minor isomer in brackets] 28.0 (q), [28.2 (q)], [36.1 (s)], [30.8 (t)], 40.05 (t), 41.0 (s), 62.8 (d) [62.8, 67.1, 67.2 (d)], 67.3, 67.4 (d), [71.9 (d)], 72.8, 75.7 (d); *m*/*z* (EI) 373 (M^+), 316, 281, 57.

The reaction was repeated using a different method, namely oxalyl chloride in the presence of a catalytic amount of Et_3N or PPh_3 in CCl_4 affording in all cases the tricyclic compound **13** as the only product.

3.7. General procedure for the diethylzinc addition to benzaldehyde

To a solution of 5 mol% of ligand in 5 mL of freshly distilled toluene cooled at 0°C, 1.5 equiv. of a 1 M solution of Et_2Zn in toluene was added. The resulting solution was stirred at room temperature for 30 min and 1.0 equiv. of benzaldehyde was then added. The reaction was monitored via TLC (hexane/EtOAc, 10:1). The reaction was quenched with 3 M HCl (5 mL) and extracted with CH_2Cl_2 (4×8 mL). The combined organic layer was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The crude was purified by preparative TLC (hexane/EtOAc, 10:1). The e.e. was determined by chiral GC: MFC800 Carlo Erba, HP Chiral CG (20% Permethylated β-Cyclodextrin), from 70 to 170°C 1.5°C/min, ret.-time 45.1 min (*R*), 46.5 min (*S*).

3.8. General procedure for the palladium-catalyzed allylic substitution

A solution of the acetate **17** (252 mg, 1.0 mmol), allylpalladium chloride dimer (9.1 mg, 0.025 mmol) and ligand (0.1 mmol) in dry CH_2Cl_2 (2 mL) was stirred at room temperature for 15 min. A solution of dimethyl malonate (396 mg, 3.0 mmol) and *N*,*O*-bis(trimethylsilyl)acetamide (BSA) (0.74 mL, 3.0 mmol) in CH_2Cl_2 (1 mL) was then added dropwise, followed by potassium acetate (2.5 mg, 0.03 mmol). The reaction mixture was degassed in three freeze-evacuate-thaw cycles and stirred at room temperature until disappearance of the starting acetate. Aqueous NH_4Cl was added, and the mixture was extracted with Et_2O. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The excess of dimethyl malonate was eliminated by bulb-to-bulb distillation. Purification of the crude by column chromatography (light petroleum/EtOAc, 5:1) gave **18**[22] as a clear oil that solidified on standing. The e.e. was determined by ^1H NMR using $Eu(hfc)_3$ as chiral shift reagent (10^{-3} m in $CDCl_3$) and by chiral HPLC: Varian ProStar, det.: UV (254 nm), Daicel Chiralcel OD, hexane/isopropanol 99.5:0.5, 0.3 mL/min, ret.-times: 72.6 min (*R*), 77.8 (*S*).

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