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Tetrahedron
Tetrahedron 63 (2007) 1907–1912

An efficient, general synthesis of racemic 2-substituted ferrocenecarboxaldehydes

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Received 29 November 2006; revised 22 December 2006; accepted 2 January 2007
Available online 4 January 2007

Abstract—A straightforward, high-yielding route to racemic 2-substituted ferrocenecarboxaldehydes has been developed. The synthesis involves the *ortho*-lithiation/electrophilic quenching of readily accessible 2-ferrocenyl-4,4-dimethyloxazoline (**2c**), followed by N-methylation, sodium borohydride-mediated reduction, and acidic hydrolysis.

1. Introduction

Ever since the seminal discovery of ferrocene in 1951,[1] the interest in novel ferrocene derivatives continues unabated.[2] In connection with a research program devoted to the development of new chiral auxiliaries and ligands based on 2-amino-2-ferrocenylalkanols,[3] we were in need of a general, high-yielding route to *racemic* 2-substituted ferrocenecarboxaldehydes. Whereas the increasing number of chiral ligands based on 1,2-disubstituted, planar-chiral ferrocene scaffolds[4] has led to several methods for the reliable, highly enantioselective preparation of 2-substituted ferrocenecarboxaldehydes,[5,6] much less attention has been paid to the synthesis of these compounds as racemic mixtures, and only a few scattered references can be found in the chemical literature concerning the non-enantioselective preparation of some specific examples.[7]

Whereas the *ortho*-metalation of 2-ferrocenyl-1,3-dioxane (**1**) (Fig. 1), followed by electrophilic trapping and acetal hydrolysis, has been used in a couple of instances for the preparation of racemic 1,2-disubstituted ferrocenes[7d,f] and could provide a priori a general route to our target racemic ferrocenecarboxaldehydes, the lithiation step must be carefully optimized in order to avoid cleavage of the dioxane ring, and usually leads to substantial amounts of the 1′,2-dilithiated derivative.[7d,3i] In contrast to this, the lithiation of 2-ferrocenyl-1,3-oxazolines, first reported almost 25 years ago,[8] takes place regiospecifically in the 2-position of the ferrocenyl moiety, so that further reaction of the metalated compounds with electrophiles affords exclusively 1,2-disubstituted ferrocenes in high yields. Most popular has been the asymmetric version of this method, independently developed in 1995 by Sammakia,[9] Richards,[10] and Uemura,[11] starting from enantiomerically pure 2-ferrocenyloxazolines (**2a**,**b**) (Fig. 1) that has allowed the stereoselective synthesis of a large number of planar-chiral ferrocenes subsequently applied in a variety of asymmetric, metal-catalyzed processes.[12] Although achiral 2-ferrocenyl-4,4-dimethyloxazoline (**2c**) has been *ortho*-lithiated in a number of instances,[13] the derivatives resulting from electrophilic trapping do not appear to have been converted into ferrocenecarboxaldehydes.[14] Taking into account the easy availability of **2c** that can be obtained[13a] in multigram scale from commercial ferrocene carboxylic acid,[15] as well as the existence of literature precedents for the transformation of 2-aryloxazolines into aryl aldehydes,[16] we decided to explore the possibility of using compound **2c** for developing an efficient and versatile route to racemic 2-substituted ferrocenecarboxaldehydes. Herein, we wish to disclose the successful experimental implementation of these ideas.

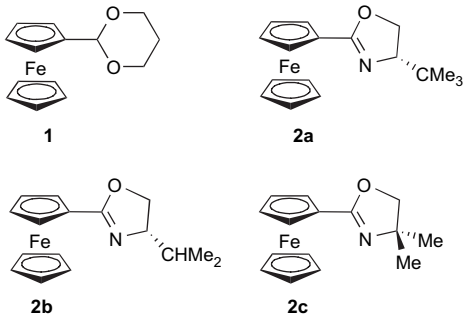

Figure 1.

Keywords: Aldehydes; Ferrocenes; *ortho*-Lithiation; Oxazolines.
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doi:10.1016/j.tet.2007.01.003

2. Results and discussion

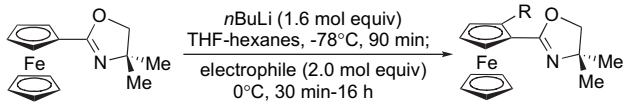
After having prepared 2-ferrocenyl-4,4-dimethyloxazoline **2c** according to the procedure described in the literature (77% overall yield from ferrocene carboxylic acid),[13a] we initiated the study of its lithiation/electrophilic trapping. We could rapidly establish that optimal conditions for this transformation involved the treatment of a solution of **2c** in anhydrous tetrahydrofuran with 1.6 mol equiv of *n*-butyllithium (1.6 M in hexanes) at −78 °C for 90 min, heating up to 0 °C and addition of 2 mol equiv of a suitable electrophile. In this way, a set of 2-substituted 1-(4,4-dimethyloxazolin-2-yl)ferrocenes **3a–i** were obtained in good to excellent yields after chromatographic purification (Table 1).

The conversion of the 2-substituted oxazolinylferrocenes into the corresponding aldehydes required a careful optimization of the reaction conditions. Thus, following a literature procedure,[16c] when oxazoline **2c** (taken as a model compound) was treated with an excess of methyl iodide in refluxing acetonitrile and the resulting *N*-methyl oxazolinium salt was reduced with sodium borohydride in ethanol, ferrocenecarboxaldehyde was obtained in low yield after hydrolysis of the intermediate *N*-methyl-2-ferrocenyloxazolidine with aqueous hydrochloric acid. Similar unsatisfactory results were recorded for oxazolines **3a** and **3c**. After some experimentation, we found that the replacement of methyl iodide/acetonitrile by methyl triflate/dichloromethane, together with the use of oxalic acid for the hydrolysis of the *N*-methyloxazolidine ring,[16e] afforded ferrocenecarboxaldehyde in 80% yield from **2c** (Scheme 1).

Satisfactorily enough, these conditions proved to be adequate for most of the previously prepared 2-substituted 2-ferrocenyloxazolines, provided that the time required for the acidic hydrolysis step was carefully monitored by TLC in order to minimize the acid-mediated decomposition of the resulting aldehydes (Table 2).

In the case of oxazoline **3f** (entry 6 in Table 2), a complex mixture of unidentified products was obtained, probably due to competitive methylation of the phosphorus atom; an attempt to circumvent this problem by previous treatment of **3f** with borane–methyl sulfide complex did not bring about any positive result. For the remaining oxazolines (including compound **3e**, in which no methylation of the selenium atom was observed; entry 5 in Table 2), the expected racemic aldehydes were isolated in ca. 80% yield. Prior to N-alkylation and reductive cleavage of the oxazoline ring, the mixture of alcohols **3h** was converted into 2-(2-vinylferrocenyl)-4,4-dimethyloxazoline **3h′** by alumina-mediated dehydration.[3i] A noteworthy feature of the present procedure is that the mild conditions of the hydrolysis step (oxalic acid) allow its use for acid-sensitive compounds like the vinylferrocene **4h′** (entry 8 in Table 2) and the ferrocenylcarbinol **4i** (entry 9 in Table 2).

Table 1. *ortho*-Lithiation/electrophilic quenching of 2-ferrocenyl-4,4-dimethyloxazoline **2c**

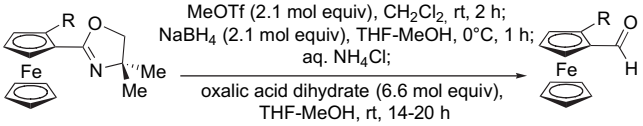


2c **3a-i** (*rac*)

Entry	Electrophile (time)[a]	R	Compound	Yield[b] (%)
1	I_2 (1 h)	I	**3a**	85 (41)[c]
2	NBS (1 h)	Br	**3b**	78
3	$ClSiMe_3$ (30 min)	TMS	**3c**	86 (40)[c]
4	$ClSnMe_3$ (30 min)	Me_3Sn	**3d**	88
5	PhSeCl (30 min)	PhSe	**3e**	89
6	Ph_2PCl (40 min)	Ph_2P	**3f**	84
7	MeI (30 min)	Me	**3g**	97
8	Ethanal (16 h)	MeCH(OH)[d]	**3h**	95[e]
9	Benzophenone (16 h)[f]	$Ph_2C(OH)$	**3i**	100

[a] Time necessary for complete reaction of the 2-lithio derivative of **2c** with the electrophile (TLC monitoring).
[b] Yield of isolated products **3a–i** after chromatographic purification.
[c] *s*-BuLi was used in the lithiation step.
[d] Diastereomeric mixture.
[e] Ref. 3i.
[f] Electrophilic quenching was performed at −35 °C.

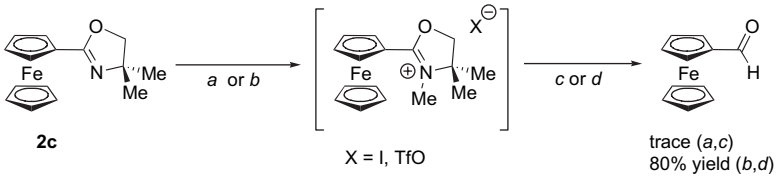
Table 2. N-methylation, reduction, and hydrolysis of 2-substituted 1-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)ferrocenes **3a–i**



3a-i (*rac*) **4a-i** (*rac*)

Entry	Oxazoline	Hydrolysis time[a] (h)	R	Aldehyde	Yield[b] (%)
1	**3a**	20	I	**4a**	80
2	**3b**	18	Br	**4b**	75
3	**3c**	15	TMS	**4c**	79
4	**3d**	15	Me_3Sn	**4d**	76
5	**3e**	14	PhSe	**4e**	82
6	**3f**	—	Ph_2P	**4f**	0
7	**3g**	20	Me	**4g**	83
8	**3h′**[c]	14	Vinyl	**4h′**	72
9	**3i**	16	$Ph_2C(OH)$	**4i**	80

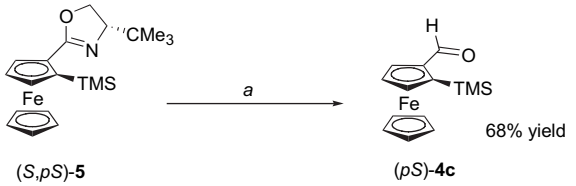
[a] Time employed for the acidic hydrolysis step.
[b] Yield of isolated products **4a–i** after chromatographic purification.
[c] Prepared from **3h** as described in Ref. 3i.



2c X = I, TfO trace (*a*,*c*) 80% yield (*b*,*d*)

Scheme 1. Reagents and conditions: (a) MeI, CH_3CN, reflux; (b) MeOTf, CH_2Cl_2, rt; (c) (i) $NaBH_4$, EtOH, rt; (ii) aq HCl, rt; (d) (i) $NaBH_4$, THF/MeOH, 0 °C, aq NH_4Cl; (ii) oxalic acid dihydrate, THF/MeOH, rt.

Finally, we would like to emphasize that this methodology can also be advantageously applied to the synthesis of highly enantiopure 2-substituted ferrocenecarboxaldehydes. Thus, (*S*,*pS*)-2-(2-trimethylsilylferrocenyl)-4-(*tert*-butyl)oxazoline **5** (94% de)[9a] was converted into (*pS*)-**4c** in 68% yield under the conditions described above (Scheme 2). It is worth noting that the yield previously described for the very similar transformation of (*S*,*pR*)-2-(2-methylferrocenyl)-4-(*tert*-butyl)oxazoline into (*pR*)-**4g** was much lower (12%).[9a,14]



Scheme 2. Reagents and conditions: (a) (i) MeOTf, CH_2Cl_2, rt, 2 h; (ii) $NaBH_4$, THF/MeOH, 0 °C, 1 h, aq NH_4Cl; (iii) oxalic acid dihydrate, THF/H_2O, rt, 20 h.

3. Conclusions

In summary, we have found that a wide range of racemic 2-substituted ferrocenecarbaldehydes can be easily obtained from readily available 2-ferrocenyl-4,4-dimethyloxazoline **2c** by means of a two-step protocol involving *ortho*-metalation with *n*-butyllithium and electrophilic quenching, followed by N-methylation (methyl triflate in methylene chloride, rt), sodium borohydride reduction (methanol/THF, 0 °C), and mild acidic hydrolysis (oxalic acid dihydrate, rt). Advantageous characteristics of this methodology (also applicable to the preparation of optically active 2-substituted ferrocenecarboxyaldehydes) are the accessibility of starting materials and reagents, reproducibly satisfactory yields, and functional group tolerance.

4. Experimental section

4.1. General materials and methods

Melting points were taken on an Electrothermal apparatus and have not been corrected. Infrared spectra were recorded in a Fourier transform mode on a Nicolet 510 FT spectrometer, using NaCl film techniques. Only the most representative wavenumbers (cm^{-1}) are reported. NMR spectra were recorded in $CDCl_3$ solution. ^1H NMR (200 MHz) and ^{13}C NMR (50.3 MHz) spectra were obtained on a Varian Gemini spectrometer; ^1H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were obtained on a Varian Mercury spectrometer. Chemical shifts (δ) are quoted in parts per million and referenced to internal TMS for ^1H NMR and to $CDCl_3$ (δ 77.0) for ^{13}C NMR; data are reported as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; coupling constants (*J*) are quoted in hertz. Low resolution chemical ionization mass spectra were recorded on an HP-5988 A spectrometer. High resolution mass spectra (HRMS) were obtained from the 'Unidad de Espectrometría de Masas de la Universidad de Santiago de Compostela'. Reactions were run in flame- or oven-dried glassware under a N_2 atmosphere. Commercially available reagents were employed as received. Dichloromethane was distilled from calcium hydride. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl. Oxazolines **2c** and **5** were obtained according to literature procedures.[9a,13a] The preparation of ferrocenyloxazolines **3h** and **3h′** has been previously described by us.[3i]

4.2. Representative procedure A for the lithiation/electrophilic trapping of 2-ferrocenyl-4,4-dimethyloxazoline 2c: *rac*-2-(2-iodoferrocenyl)-4,4-dimethyloxazoline 3a

To a cold (−78 °C), stirred solution of the 2-ferrocenyloxazoline **2c** (100 mg, 0.35 mmol) in anhydrous THF (5.6 mL), under nitrogen atmosphere, a 1.6 M solution of *n*-butyllithium in hexanes (0.40 mL, 0.52 mmol) was added with the aid of a syringe and the resulting solution was stirred at the same temperature for 1.5 h. After warming up to 0 °C, freshly sublimed iodine (31 mg, 0.71 mmol) was added in one portion, and the stirring was maintained for 1 h at the same temperature. At this point, TLC monitoring showed the complete disappearance of the starting oxazoline. After the addition of saturated aqueous sodium sulfite (15 mL) at rt, the phases were separated, and the aqueous phase was extracted with diethyl ether (3×15 mL). The combined extracts were dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent, hexanes/ethyl acetate mixtures of increasing polarity) to give the title compound **3a** (hexanes/ethyl acetate 4:1, 123 mg, 85% yield) as a dense red-colored oil that solidified in the fridge. The IR and the ^1H NMR spectra of this compound fully coincided with those described in the literature for the (*pS*)-enantiomer.[13a] ^1H NMR ($CDCl_3$, 200 MHz) δ 1.29 (6H, s, $2CH_3$), 4.09–4.24 (2H, m, CH_2), 4.14 (5H, s, Fc*H*), 4.28–4.30 (1H, m, Fc*H*), 4.51–4.53 (1H, m, Fc*H*), 4.72–4.74 (1H, m, Fc*H*).

4.2.1. *rac*-2-(2-Bromoferrocenyl)-4,4-dimethyloxazoline 3b. Prepared by the same method as above in 78% yield from **2c** (0.35 mmol) and from *N*-bromosuccinimide (0.71 mmol). Spectral data were coincident with those previously described in the literature.[13d] ^1H NMR ($CDCl_3$, 200 MHz) δ 1.27 (6H, s, $2CH_3$), 4.02 (2H, m, CH_2), 4.19 (5H, s, Fc*H*), 4.24 (1H, m, Fc*H*), 4.35 (1H, br s, Fc*H*), 4.41 (1H, br s, Fc*H*).

4.3. Representative procedure B for the lithiation/electrophilic trapping of 2-ferrocenyl-4,4-dimethyloxazoline 2c: *rac*-2-(2-trimethylsilylferrocenyl)-4,4-dimethyloxazoline 3c[13c]

To a cold (−78 °C), stirred solution of the ferrocenyloxazoline **2c** (500 mg, 1.8 mmol) in anhydrous THF (25 mL), under nitrogen atmosphere, a 1.6 M solution of *n*-butyllithium in hexanes (1.7 mL, 2.7 mmol) was added with the aid of a syringe and the resulting solution was stirred at the same temperature for 1.5 h. After warming up to 0 °C, freshly distilled chlorotrimethylsilane (0.27 mL, 2.1 mmol) was added dropwise, and the stirring was maintained for 30 min at the same temperature. At this point, TLC monitoring showed the complete disappearance of the starting oxazoline. After the addition of saturated aqueous ammonium chloride (15 mL)

at rt, the phases were separated, and the aqueous phase was extracted with ethyl acetate (4×15 mL). The combined extracts were dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent, hexanes/ethyl acetate mixtures of increasing polarity) to give the title compound **3c**[13c] (hexanes/ethyl acetate 6.3:1, 542 mg, 86% yield) as a dense red-colored oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.30 (9H, s, Si(CH_3)$_3$), 1.33 (6H, s, 2CH_3), 3.97 (2H, m, CH_2), 4.17 (5H, s, Fc*H*), 4.24 (1H, m, Fc*H*), 4.44 (1H, br s, Fc*H*), 4.90 (1H, br s, Fc*H*). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 27.0 (CH_3), 27.5 (CH_3), 27.8 (CH_3), 66.7 (C), 67.3 (C), 69.0 (CH), 72.5 (CH), 75.7 (CH), 76.3 (CH), 78.0 (CH_2), 135.0 (C), 163.9 (C).

4.3.1. *rac*-2-(2-Trimethylstannylferrocenyl)-4,4-dimethyloxazoline 3d. Prepared by the same method as above in 88% yield from **2c** (0.70 mmol) and from trimethyltin chloride (0.84 mmol). Red-colored oil. IR (film): ν 2968, 1653, 1123, 1190, 767. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.27 (9H, s, Sn(CH_3)$_3$), 0.42 (3H, s, CH_3), 1.31 (3H, s, CH_3), 3.98 (2H, br s, CH_2), 4.14 (5H, s, Fc*H*), 4.23 (1H, m, Fc*H*), 4.48 (1H, m, Fc*H*), 4.90 (1H, br s, Fc*H*). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.0 (CH_3), 28.39 (CH_3), 28.41 (CH_3), 31.3 (CH), 60.3 (CH), 68.9 (C), 69.4 (C), 70.3 (CH), 73.1 (CH), 78.0 (CH_2), 135.0 (C), 165.0 (C). HRMS (CI, NH_3): *m*/*z* calcd for [M+H]$^+$ $C_{18}H_{26}$FeNOSn: 448.0308; found: 448.0380.

4.3.2. *rac*-2-(2-Phenylselenylferrocenyl)-4,4-dimethyloxazoline 3e. Prepared by the same method as above in 89% yield from **2c** (0.35 mmol) and from phenylselenyl chloride (0.42 mmol). Red-colored oil. IR (film): ν 3095, 2965, 1654, 1296, 1103, 969, 821. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35 (6H, s, 2CH_3), 2.16 (3H, m, Ar*H*), 4.00 (2H, br s, CH_2), 4.18 (5H, s, Fc*H*), 4.21 (1H, m, Fc*H*), 4.32 (1H, m, Fc*H*), 4.75 (1H, br s, Fc*H*), 7.23 (1H, m, Ar*H*), 7.45 (1H, m, Ar*H*). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 27.0 (C), 28.39 (CH_3), 28.41 (CH_3), 31.1 (CH), 68.2 (C), 69.9 (C), 70.9 (CH), 71.0 (CH), 75.1 (CH), 78.1 (CH), 78.9 (CH_2), 127.1 (CH), 129.6 (CH), 129.8 (CH), 134.3 (C), 164.5 (C). HRMS (CI, NH_3): *m*/*z* calcd for [M+H]$^+$ $C_{21}H_{22}$FeNOSe: 440.0138; found: 440.0211.

4.3.3. *rac*-2-(2-Diphenylphosphanylferrocenyl)-4,4-dimethyloxazoline 3f. Prepared by the same method as above in 84% yield from **2c** (0.35 mmol) and from chlorodiphenylphosphine (0.42 mmol). Brown-colored solid; mp=177–178 °C. Spectral data for this compound coincided with those described in the literature for the (*pS*)-enantiomer.[17] ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.18 (3H, s, CH_3), 1.21 (3H, s, CH_3), 3.55 (1H, d, *J*=8.0 Hz, C*H*H′), 3.68 (1H, m, Fc*H*), 4.02 (1H, d, *J*=8.0 Hz, CH*H*′), 4.19 (5H, s, Fc*H*), 4.39 (1H, t, *J*=2.6 Hz, Fc*H*), 4.99 (1H, m, Fc*H*), 7.18–7.52 (10H, m, Ar*H*). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 27.8 (CH_3), 28.1 (CH_3), 66.5 (CH), 66.9 (CH), 67.6 (CH), 69.6 (C), 70.8 (C), 72.1 (CH), 74.5 (CH), 76.4 (CH), 77.0 (CH), 77.6 (CH_2), 90.0 (CH), 127.8 (CH), 128.2 (CH), 129.9 (CH), 132.1 (CH), 132.4 (CH), 132.6 (CH), 135.0 (C), 163.8 (C).

4.3.4. *rac*-2-(2-Methylferrocenyl)-4,4-dimethyloxazoline 3g. Prepared by the same method as above in 97% yield from **2c** (0.35 mmol) and from pre-purified (filtration through a short pad of diphosphorus pentoxide–silica gel) iodomethane (0.52 mmol). Red-orange oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.36 (6H, s, 2CH_3), 2.24 (3H, s, CH_3), 4.08 (2H, br s, CH_2), 4.10 (5H, s, Fc*H*), 4.17–4.18 (1H, m, Fc*H*), 4.19–4.23 (1H, m, Fc*H*), 4.70 (1H, br s, Fc*H*). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 13.8 (CH_3), 28.4 (CH_3), 67.3 (CH), 69.0 (C), 69.6 (C), 70.3 (CH), 71.0 (CH), 78.7 (CH_2), 134.8 (C), 164.0 (C). HRMS (CI, NH_3): *m*/*z* calcd for [M+H]$^+$ $C_{16}H_{20}$FeNO: 298.0894; found: 298.0903.

4.3.5. *rac*-2-(2-Diphenylhydroxymethylferrocenyl)-4,4-dimethyloxazoline 3i. Prepared by the same method as above in 97% yield from **2c** (0.88 mmol) and from benzophenone (1.32 mmol). Red-colored oil. Spectral data coincided with those previously described for the (*pR*)-enantiomer.[13a] ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.67 (3H, s, CH_3), 1.30 (3H, s, CH_3), 3.64–3.65 (1H, m, Fc*H*), 4.00 (2H, s, CH_2), 4.21–4.22 (1H, m, Fc*H*), 4.28 (5H, s, Fc*H*), 4.67–4.69 (1H, m, Fc*H*), 7.07–7.15 (5H, m, Ar*H*), 7.21–7.35 (3H, m, Ar*H*), 7.51–7.54 (2H, m, Ar*H*).

4.4. Representative procedure for the preparation of ferrocenecarboxaldehydes from 2-ferrocenyl-4,4-dimethyloxazolines: ferrocenecarboxaldehyde from 2c

To a solution of 2-ferrocenyl-4,4-dimethyloxazoline **2c** (100 mg, 0.35 mmol) in anhydrous dichloromethane (3.8 mL), methyl triflate (0.10 mL, 0.73 mmol) was added in one portion and the resulting mixture was vigorously stirred for 2 h at rt. During this time, the color of the solution changed from orange to deep red. After cooling to 0 °C, a solution of sodium borohydride (28 mg, 0.73 mmol) in 3.2:1 THF/MeOH (2 mL) was added dropwise. After stirring for 1 h at the same temperature, the reaction was quenched by the dropwise addition of aqueous saturated ammonium chloride (3.8 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (3×4 mL). The combined organic extracts were washed with brine (5 mL), dried over magnesium sulfate, and evaporated under reduced pressure. The red-colored solid obtained was stirred with a solution of oxalic acid dihydrate (293 mg, 2.31 mmol) in 3:1 THF/MeOH (3.5 mL) for 18 h at rt. After the addition of diethyl ether (3.5 mL) the reaction mixture was washed with aqueous saturated sodium bicarbonate (3 mL) and with brine (3 mL), dried over magnesium sulfate, and the solvents were distilled off in vacuo. Chromatographic purification (silica gel, 9:1 hexanes/ethyl acetate) afforded 60 mg (80% yield) of ferrocenecarboxaldehyde as a red-colored solid. 2-Substituted ferrocenecarboxaldehydes **4a–i** were obtained (with the sole exception of **4f**) in a similar way, although the optimal time for the acidic hydrolysis step was different for each compound (see Table 2).

4.4.1. *rac*-2-Iodoferrocenecarboxaldehyde 4a.[6f,18] Obtained in 79% yield from **3a** (0.24 mmol) by the procedure described above, after chromatographic purification (silica gel, 5.6:1 hexanes/ethyl acetate) as a brownish-red oil. Spectral data for this compound were coincident with those described in the literature for the (*pS*)-enantiomer.[6f] ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.27 (5H, s, Fc*H*), 4.67 (1H, m, Fc*H*), 4.81 (1H, m, Fc*H*), 4.88 (1H, m, Fc*H*), 10.02 (1H, s, C*H*O).

4.4.2. *rac*-2-Bromoferrocenecarboxaldehyde 4b. Obtained in 75% yield from **3b** (0.24 mmol) by the procedure described above, after chromatographic purification (silica gel, 5.6:1 hexanes/ethyl acetate) as a red-colored oil. Spectral data for this compound were coincident with those described in the literature for the (*pS*)-enantiomer.[5b,6f] ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.31 (5H, s, Fc*H*), 4.59 (1H, m, Fc*H*), 4.79 (1H, br s, Fc*H*), 4.83 (1H, br s, Fc*H*), 10.14 (1H, s, C*H*O).

4.4.3. *rac*-2-Trimethylsilylferrocenecarboxaldehyde 4c. Obtained in 79% yield from **3c** (0.29 mmol) by the procedure described above, after chromatographic purification (silica gel, 20:1 hexanes/ethyl acetate) as a waxy red-colored solid. Spectral data for this compound were coincident with those described in the literature for the (*pS*)-enantiomer.[5b,6h] ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.33 (9H, s, Si(C*H*$_3$)$_3$), 4.26 (5H, s, Fc*H*), 4.53 (1H, br s, Fc*H*), 4.71 (1H, m, Fc*H*), 4.98 (1H, br s, Fc*H*), 10.10 (1H, s, C*H*O).

4.4.4. *rac*-2-Trimethylstannylferrocenecarboxaldehyde 4d. Obtained in 76% yield from **3d** (0.23 mmol) by the procedure described above, after chromatographic purification (silica gel, 24:1 hexanes/ethyl acetate) as a deep red-colored oil. Spectral data were coincident to those reported for the optically active compound.[19] ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.27 (9H, s, Sn(C*H*$_3$)$_3$), 4.19 (5H, s, Fc*H*), 4.45 (1H, br s, Fc*H*), 4.56 (1H, m, Fc*H*), 4.77 (1H, m, Fc*H*), 10.50 (1H, s, C*H*O).

4.4.5. *rac*-2-Phenylselenylferrocenecarboxaldehyde 4e. Obtained in 82% yield from **3e** (0.23 mmol) by the procedure described above, after chromatographic purification (silica gel, 24:1 hexanes/ethyl acetate) as a deep red-colored oil. IR (film): ν 3088, 2934, 1694, 1214, 1083, 984, 832. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.12 (5H, s, Fc*H*), 4.29 (1H, m, Fc*H*), 4.35 (1H, m, Fc*H*), 4.58 (1H, br s, Fc*H*), 7.23 (3H, m, Ar*H*), 7.45 (2H, m, Ar*H*), 9.65 (1H, s, C*H*O). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 32.1 (CH), 68.5 (C), 70.4 (CH), 71.0 (CH), 75.1 (CH), 78.1 (C), 127.0 (CH), 129.6 (CH), 129.8 (CH), 134.3 (C), 190.5 (CH). HRMS (CI, NH_3): *m*/*z* calcd for $[M+H]^+$ $C_{17}H_{15}FeOSe$: 368.9403; found: 368.9492.

4.4.6. *rac*-2-Methylferrocenecarboxaldehyde 4g. Obtained in 83% yield from **3g** (0.34 mmol) by the procedure described above, after chromatographic purification (silica gel, 9:1 hexanes/ethyl acetate) as a red-brown oil. Spectral data were coincident to those reported for the optically active compound.[9a,20] ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.23 (3H, s, C*H*$_3$), 4.17 (5H, s, Fc*H*), 4.44 (1H, m, Fc*H*), 4.67 (2H, m, Fc*H*), 10.08 (1H, s, C*H*O). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 13.5 (CH_3), 69.4 (C), 70.2 (CH), 71.0 (CH), 75.0 (CH), 77.1 (CH), 78.5 (C), 182.0 (CH).

4.4.7. *rac*-2-Vinylferrocenecarboxaldehyde 4h′. Obtained in 72% yield from **3h′**[3i] (0.32 mmol) by the procedure described above, after chromatographic purification (neutral alumina, 4.9:1 hexanes/ethyl acetate) as a red-brown oil. Spectral data were coincident to those previously reported for the (*pS*)-enantiomer.[6d,11a] ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.13 (5H, s, Fc*H*), 4.55 (1H, t, *J*=2.5 Hz, Fc*H*), 4.74 (1H, m, Fc*H*), 4.80 (1H, m, Fc*H*), 5.16 (1H, d, *J*=12.0 Hz, =C*H*H′), 5.44 (1H, d, *J*=17.5 Hz, =CH*H*′), 6.87 (1H, dd, *J*=12.0 and 17.5 Hz, Fc–*H*C=), 10.20 (1H, s, C*H*O).

4.4.8. *rac*-2-(Diphenylhydroxymethyl)ferrocenecarboxaldehyde 4i.[21] Obtained in 80% yield from **3i** (0.22 mmol) by the procedure described above, after chromatographic purification (silica gel, 5.7:1 hexanes/ethyl acetate) as a red-colored solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.64–3.65 (1H, br s, O*H*), 4.21–4.22 (1H, m, Fc*H*), 4.28 (5H, s, Fc*H*), 4.68 (1H, m, Fc*H*), 4.73–4.77 (1H, m, Fc*H*), 7.07–7.15 (5H, m, Ar*H*), 7.21–7.35 (3H, m, Ar*H*), 7.51–7.54 (2H, m, Ar*H*), 10.06 (1H, s, C*H*O). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 66.5 (CH), 66.9 (CH), 67.6 (CH), 69.6 (CH), 74.8 (C), 76.6 (CH), 77.1 (CH), 78.9 (C), 101.6 (C), 126.2 (CH), 126.5 (CH), 127.0 (CH), 127.2 (CH), 127.5 (CH), 127.7 (CH), 187.0 (CH). Some signals corresponding to quaternary carbons were too weak to be observed.

4.4.9. (*pS*)-2-Trimethylsilylferrocenecarboxaldehyde (*pS*)-4c. Obtained in 68% yield from **5**[13a] (9.6 mmol) by the procedure described above, after chromatographic purification (silica gel, hexanes/ethyl acetate) as a waxy red-orange solid. $[\alpha]_D$ −199 (*c* 0.24, EtOH) [lit.:[5b] $[\alpha]_D$ −202 (*c* 0.24, EtOH)].

Acknowledgements

We gratefully acknowledge financial support from Ministerio de Ciencia y Tecnología (DGI, project BQU2003-03426). M.R. thanks the DURSI (Generalitat de Catalunya) for a pre-doctoral fellowship.

References and notes

1. (a) Keally, T. J.; Pauson, P. L. *Nature* **1951**, *168*, 1039; (b) Wilkinson, G.; Rosenblum, M.; Whiting, M. C.; Woodward, R. B. *J. Am. Chem. Soc.* **1952**, *74*, 2125.
2. (a) *Ferrocenes. Homogeneous Catalysis, Organic Synthesis, Materials Science*; Hayashi, T., Togni, A., Eds.; VCH: Weinheim, Germany, 1995; (b) vanStaveren, D. R.; Metzler-Nolte, N. *Chem. Rev.* **2004**, *104*, 5931; (c) Beer, P. D. *Adv. Inorg. Chem.* **1992**, *39*, 79.
3. (a) Catasús, M.; Bueno, A.; Moyano, A.; Maestro, M. A.; Mahía, J. *J. Organomet. Chem.* **2002**, *642*, 212; (b) Catasús, M.; Moyano, A.; Aggarwal, V. K. *Tetrahedron Lett.* **2002**, *43*, 3475; (c) Moreno, R. M.; Bueno, A.; Moyano, A. *J. Organomet. Chem.* **2002**, *660*, 62; (d) Moyano, A.; Rosol, M.; Moreno, R. M.; López, C.; Maestro, M. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1865; (e) Rosol, M.; Moyano, A. *J. Organomet. Chem.* **2005**, *609*, 2328; (f) Bueno, A.; Moreno, R. M.; Moyano, A. *Tetrahedron: Asymmetry* **2005**, *16*, 1763; (g) Moreno, R. M.; Bueno, A.; Moyano, A. *J. Org. Chem.* **2006**, *71*, 2528; (h) Moreno, R. M.; Moyano, A. *Tetrahedron: Asymmetry* **2006**, *17*, 1104; (i) Bueno, A.; Rosol, M.; García, J.; Moyano, A. *Adv. Synth. Catal.* **2006**, *348*, 2590.
4. (a) Togni, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *35*, 1475; (b) Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377; (c) Sutcliffe, O. B.; Bryce, M. R. *Tetrahedron: Asymmetry* **2003**, *14*, 2297; (d) Dai, L.-X.; Tu, T.; You, S.-L.; Deng, W.-P.; Hou, X.-L. *Acc. Chem. Res.* **2003**, *36*, 659; (e) Barbaro, P.; Bianchini, C.; Giambastiani, G.; Parisel, S. L.

Coord. Chem. Rev. **2004**, *248*, 2131; (f) Guiry, P. J.; Saunders, C. P. *Adv. Synth. Catal.* **2004**, *346*, 497; (g) Atkinson, R. C. J.; Gibson, V. C.; Long, N. J. *Chem. Soc. Rev.* **2004**, *33*, 313.

5. (a) Riant, O.; Samuel, O.; Kagan, H. B. *J. Am. Chem. Soc.* **1993**, *115*, 5835; (b) Riant, O.; Samuel, O.; Flessner, T.; Taudien, S.; Kagan, H. B. *J. Org. Chem.* **1997**, *62*, 6733; (c) Riant, O.; Argouarch, G.; Guillaneux, D.; Kagan, H. B. *J. Org. Chem.* **1998**, *63*, 3511.
6. (a) Togni, A.; Rihs, G. *Organometallics* **1993**, *12*, 3368; (b) Enders, D.; Peters, R.; Lochtman, R.; Rusink, J. *Synlett* **1997**, 1462; (c) Lagneau, N. M.; Chen, Y.; Robben, P. M.; Sin, H.-S.; Takasu, K.; Chen, J.-S.; Robinson, P. D.; Hua, D. H. *Tetrahedron* **1998**, *54*, 7301; (d) Lu, X.; Chen, G. *Tetrahedron* **1998**, *54*, 12539; (e) Patti, A.; Lambusta, D.; Piattelli, M.; Nicolosi, G. *Tetrahedron: Asymmetry* **1998**, *9*, 3073; (f) Widhalm, M.; Nettekoven, U.; Mereiter, K. *Tetrahedron: Asymmetry* **1999**, *10*, 4369; (g) Janowska, I.; Zakrzewski, J. *Tetrahedron: Asymmetry* **2003**, *14*, 3271; (h) Fleischer, I.; Toma, S. *Collect. Czech. Chem. Commun.* **2004**, *69*, 330; (i) Alexakis, A.; Tomassini, A.; Andrey, O.; Bernardinelli, G. *Eur. J. Org. Chem.* **2005**, 1332.
7. (a) Morris, D. R.; Rockett, B. W. *J. Organomet. Chem.* **1972**, *35*, 179; (b) Kovar, R. F.; Rausch, M. D. *J. Organomet. Chem.* **1972**, *35*, 351; (c) Malfait, S.; Pélinski, L.; Maciejewski, L.; Brocard, J. *Synlett* **1997**, 830; (d) Steffen, W.; Laskowski, M.; Collins, G.; Bunz, U. H. F. *J. Organomet. Chem.* **2001**, *630*, 132; (e) Taylor, C. J.; Roca, F. X.; Richards, C. J. *Synlett* **2005**, 2159; (f) Mamane, V.; Fort, I. *J. Org. Chem.* **2005**, *70*, 8220.
8. Schmitt, G.; Klein, P.; Ebertz, W. *J. Organomet. Chem.* **1982**, *234*, 63.
9. (a) Sammakia, T.; Latham, H. A.; Schaad, D. R. *J. Org. Chem.* **1995**, *60*, 10; (b) Sammakia, T.; Latham, H. A. *J. Org. Chem.* **1995**, *60*, 6002; (c) Sammakia, T.; Latham, H. A. *J. Org. Chem.* **1996**, *61*, 1629.
10. (a) Richards, C. J.; Damalidis, T.; Hibbs, D. B.; Hursthouse, M. B. *Synlett* **1995**, 74; (b) Richards, C. J.; Mulvanet, A. W. *Tetrahedron: Asymmetry* **1996**, *7*, 1419.
11. (a) Nishibayashi, Y.; Uemura, S. *Synlett* **1995**, 79; (b) Nishibayashi, Y.; Segawa, K.; Ohe, K.; Hidai, M.; Uemura, S. *J. Organomet. Chem.* **1997**, *545–546*, 381.
12. For some leading references, see:. (a) Richards, C. J.; Hibbs, D. E.; Hursthouse, M. B. *Tetrahedron Lett.* **1995**, *36*, 3745; (b) Nishibayashi, Y.; Segawa, K.; Takada, H.; Ohe, K.; Uemura, S. *Chem. Commun.* **1996**, 487; (c) Sammakia, T.; Stangeland, E. M. *J. Org. Chem.* **1997**, *62*, 6104; (d) Ahn, K. H.; Cho, C.-W.; Park, J.; Lee, S. *Tetrahedron: Asymmetry* **1997**, *8*, 1179; (e) Stangeland, E.; Sammakia, T. *Tetrahedron* **1997**, *53*, 16053; (f) Donde, Y.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 2933; (g) Bolm, C.; Muñiz, K.; Hildebrand, J. P. *Org. Lett.* **1999**, *1*, 491; (h) Deng, W.-P.; Hou, X.-L.; Dai, L.-X.; Yu, Y.-H.; Xia, W. *Chem. Commun.* **2000**, 285; (i) Deng, W.-P.; You, S.-L.; Hou, X.-L.; Dai, L.-X.; Yu, Y.-H.; Xia, W.; Sun, J. *J. Am. Chem. Soc.* **2001**, *123*, 6508; (j) Bolm, C.; Kesselgruber, M.; Granz, A.; Hermanns, N.; Hildebrand, J. P. *New J. Chem.* **2001**, *25*, 13; (k) Kiely, D.; Guiry, P. J. *Tetrahedron Lett.* **2002**, *43*, 9545; (l) Bolm, C.; Rudolph, J. *J. Am. Chem. Soc.* **2002**, *124*, 14850; (m) Nishibayashi, Y.; Yamauchi, A.; Onodera, G.; Uemura, S. *J. Org. Chem.* **2003**, *68*, 5875; (n) Tu, T.; Hou, X.-L.; Dai, L.-X. *Org. Lett.* **2003**, *5*, 3651; (o) Hou, X.-L.; Sun, N. *Org. Lett.* **2004**, *6*, 4399; (p) Anderson, C. E.; Donde, Y.; Douglas, C. J.; Overman, L. E. *J. Org. Chem.* **2005**, *70*, 648; (q) Özçubukçu, S.; Schmidt, F.; Bolm, C. *Org. Lett.* **2005**, *7*, 1407; (r) Gao, W.; Zhang, X.; Raghunath, M. *Org. Lett.* **2005**, *7*, 4241; (s) Yan, X.-X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X.-L.; Wu, Y.-D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1979; (t) Geisler, F. M.; Helmchen, G. *J. Org. Chem.* **2006**, *71*, 2486; (u) Onodera, G.; Nishibayashi, Y.; Uemura, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 3819.
13. (a) Bolm, C.; Muñiz-Fernández, K.; Seger, A.; Raabe, G.; Günther, K. *J. Org. Chem.* **1998**, *63*, 7860; (b) Salter, R.; Pickett, T. E.; Richards, C. J. *Tetrahedron: Asymmetry* **1998**, *9*, 4239; (c) Pickett, T. E.; Richards, C. J. *Tetrahedron: Asymmetry* **1999**, *10*, 4095; (d) Pickett, T. E.; Roca, F. X.; Richards, C. J. *J. Org. Chem.* **2003**, *68*, 2592.
14. For an isolated example of the conversion of a chiral 2-ferrocenyloxazoline into scalemic 2-methylferrocenecarboxaldehyde, see Ref. 9a. Moreover, this procedure involves the use of the relatively expensive reagent K-Selectride®.
15. Alternatively, ferrocene carboxylic acid can be obtained from ferrocene by a procedure described in *Organic Syntheses* Reeves, P. C. *Org. Synth.* **1977**, *56*, 28.
16. (a) Nordin, I. C. *J. Heterocycl. Chem.* **1966**, *3*, 531; (b) Wilson, S. R.; Mao, D. T.; Khatri, H. N. *Synth. Commun.* **1980**, 17; (c) Fleming, I.; Morgan, I. T.; Sarkar, A. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2749; (d) Meyers, A. I.; Willemsem, J. J. *Tetrahedron* **1998**, *54*, 10493; (e) Clayden, J.; Kenworthy, M. N. *Org. Lett.* **2002**, *4*, 787.
17. You, S.-L.; Hou, X.-L.; Dai, L.-X.; Yu, Y.-H.; Xia, W. *J. Org. Chem.* **2002**, *67*, 4684.
18. For an early report on the preparation of *rac*-**4a** (described as a very unstable oil and not fully characterized), see: Ref. 7b.
19. Troitskaya, L. L.; Bulygina, L. A.; Sokolov, V. I. *Izv. Akad. Nauk, Ser. Khim.* **1994**, 1111.
20. Abiko, A.; Wang, G. *Tetrahedron* **1998**, *54*, 11405.
21. Peet, J. H.; Rockett, B. W. *J. Chem. Soc., Perkin Trans. 1* **1973**, 106.