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Selective synthesis of ferrocenes

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Abstract

We have developed a new *one pot* procedure for the selective functionalization of the 1′ position in ferrocenecarbaldehyde, with fair yields (up to 70%) and good regioselectivity (> 90/10). Our method uses lithium *N*-methylpiperazide as a temporary protecting group of the aldehyde function and directing group for lithiation on the unsubstituted cyclopentadienyl ring of ferrocene. The extension of this new method with enantiomerically pure 2-substituted ferrocenecarbaldehydes provides an easy access to various enantiomerically pure 1,2,1′-trisubstituted ferrocenes with three different groups. Finally, when applying our method for the lithiation of 1,1′-ferrocenedicarbaldehyde with a chiral amine, we found a *one pot* synthesis of 1,2,1′,2′-tetrasubstituted C_2-symmetrical ferrocenes with very high enantiomeric excesses (> 99%). Furthermore, changing the experimental conditions allows us to obtain 1,2,1′-trisubstituted ferrocenes with a very good enantioselectivity (up to 96%). The first chiral enantiomerically pure 2-substituted 1,1′-(*β-oxa*-trimethylene)ferrocenes and the first chiral enantiomerically pure C_2-symmetrical-disubstituted 1,1′-(*β-oxa*-trimethylene)ferrocene were also synthesized.

Keywords: Iron; Chiral ferrocenes; One pot synthesis; Chiral ferrocenophanes

1. Introduction

New methods to obtain selectively, various and especially chiral, ferrocenyl structures are of great interest because of the booming involvement of ferrocene derivatives in various fields [1] such as organic synthesis, or materials chemistry (in particular, materials for nonlinear optics) [2] and in particular asymmetric catalysis [3]. Amongst the numerous ferrocenyl ligands, Scheme 1 discloses some families of ligands which were involved in particularly efficient asymmetric catalysis (hydrogenation, allylic substitution, cross coupling, Michael reaction, …) [4].

Since the discovery of ferrocene by Pauson et al. [5] in 1951, the chemistry of ferrocene derivatives was widely developed allowing access to numerous structures. But many synthetic challenges remain as for the obtention of chiral enantiomerically pure compounds. In this review, we want to report new access to enantiomerically pure di, tri and tetrasubstituted ferrocenes with a particular focus on ferrocenes with planar chirality.

2. Synthesis of disubstituted ferrocenes

Several efficient methods for the synthesis of chiral 1,2-disubstituted ferrocenes based on diastereoselective ortholithiation of ferrocenyl derivatives containing chiral directing groups (CDG) have been already reported (see Scheme 2). The CDG may be a tertiary amine [6], an acetal [7], a sulfoxide [8], or more recently an oxazoline [9].

In this strategy, it is necessary to synthesize the ferrocene moieties bearing the CDG. This synthesis needs several steps and sometimes is tedious. To avoid this problem, very recently were reported enantioselective ortholithiation of non-chiral monosubstituted fer-

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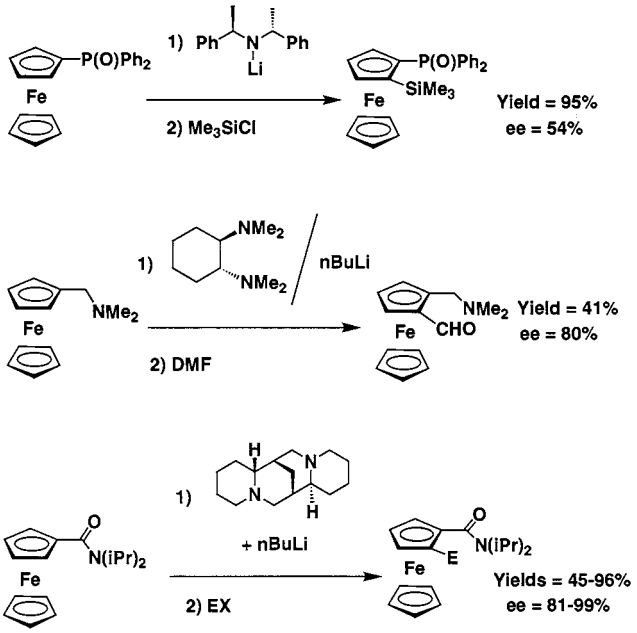
rocenes (direct methods) [10] using chiral tertiary amines as additives (see Scheme 3), to obtain the disubstituted ferrocenes with sometimes very high enantioselectivities (up to 99%ee) ([10]b).

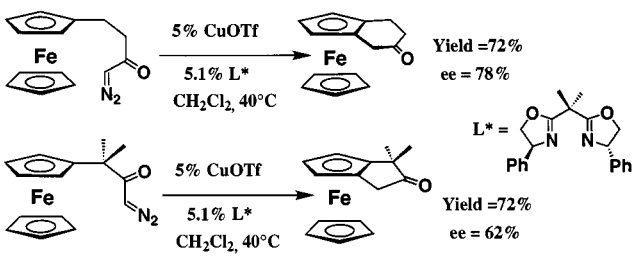
Only a few months ago was described an efficient synthesis of enantiomerically enriched ferrocenes with planar chirality using a new strategy: the insertion of carbenoids into Cp–H bond (see Scheme 4) [11].

To our concern, we tried to find a direct way to enantiomerically enriched 1,2-substituted ferrocenes by direct *one pot* functionalization of ferrocenecarbaldehyde. Having in mind the efficient synthesis of ortho-substituted benzaldehyde by using an aminoalkoxide as a temporary directing group for the ortholithiation and as a temporary protecting group of the aldehyde function in the *one pot* procedure (see Scheme 5) described by Comins et al. [12] in 1981, we thought that a similar strategy on ferrocenecarbaldehyde should yield 2-substituted ferrocenecarbaldehydes according to Scheme 6 and that the use of chiral amine would yield enantiomerically enriched products [13].

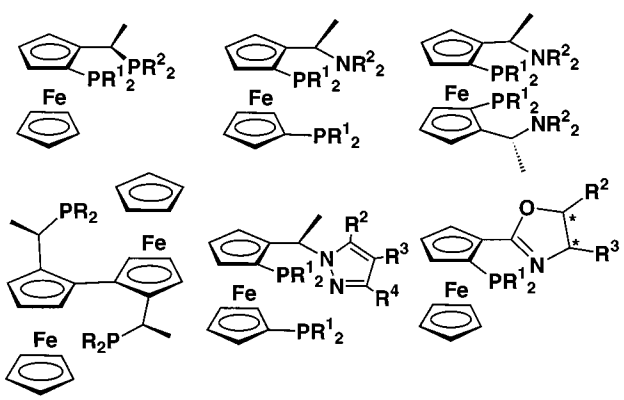
By changing the experimental conditions (temperature, solvent, …) and especially the base (*t*-BuLi vs. *n*-BuLi), we found that it is possible to succeed in the monofunctionalization of ferrocenecarbaldehyde (see Table 1) [14] but the major product is the 1,1′-substituted species (**1**) (see Scheme 7)! The yields are often good unless using sterically hindered and low reacting electrophile such as nBuI or handling a product with a low stability (see for example, Table 1, entry 9). The regioselectivity is high ((**1**)/(**2**) at least 90/10!) and no other compounds (other regioisomers, difunctionalized products, …) were observed.



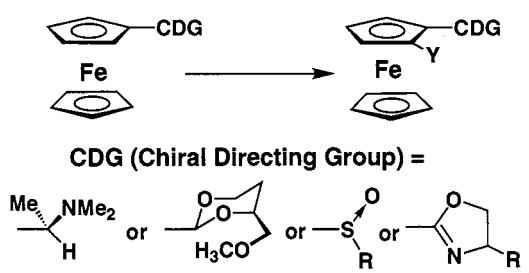
Scheme 3.



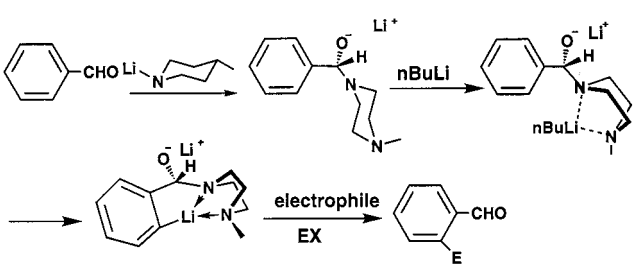
Scheme 4.



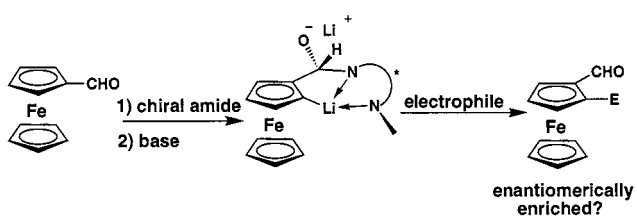
Scheme 1.



Scheme 2.



Scheme 5.

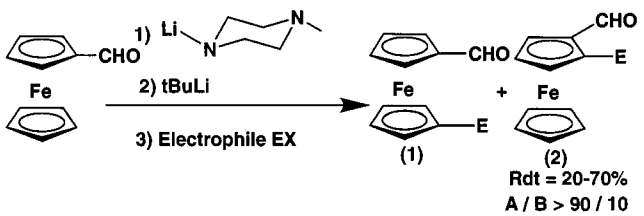


Scheme 6.

Table 1
Substitution of ferrocenecarboxaldehyde[a,b]

Entry	Electrophile	Product	Yield (%)	(**1**)/(**2**)
1	MeI	Fc′–Me	66	90/10
2	EtI	Fc′–Et	44	90/10
3	nBuI	Fc′–nBu	<5	—
4	Me_3SiCl	Fc′–$SiMe_3$	69	90/10
5	Bu_3SnCl	Fc′–$SnBu_3$	56	96/4
6	Ph_2PCl	Fc′–PPh_2	22	—
7	BCl_3	Fc′–$B(OH)_2$	21–48	92/8
8	CH_2I_2	Fc′–I	50	92/8
9	DMF	Fc′–CHO	17	86/14

[a] The reaction is run in THF with *t*-Buli as a base for 1 h at 0°C.
[b] Fc′ is $(OHC–C_5H_4)Fe(C_5H_4)$.



Scheme 7.

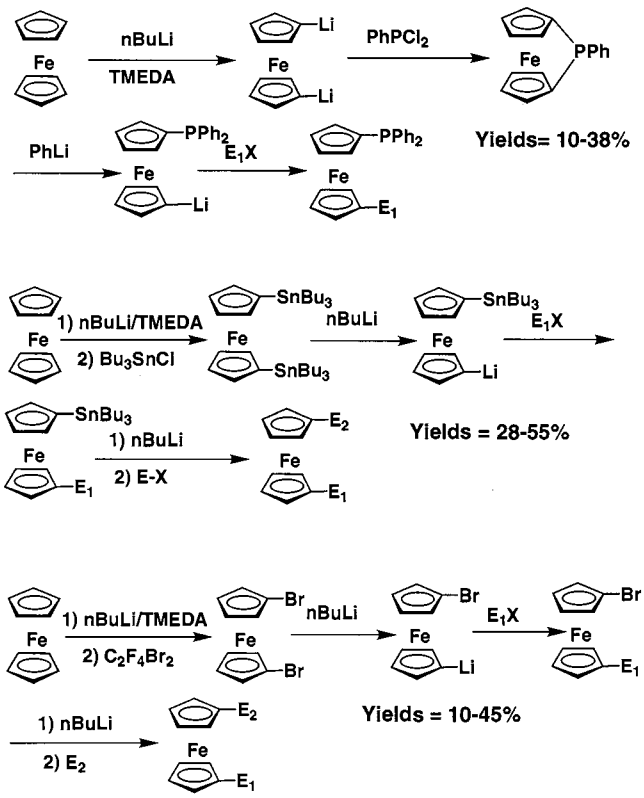
So we have discovered an efficient and straightforward method to obtain a wide range of 1,1′-disubstituted ferrocenes with two different groups by a *one pot* procedure starting from the cheap and commercially available ferrocenecarboxaldehyde. This method provides a useful alternative to existing methods with phosphorus [15], tin [16] or bromo [17] compounds based on the functionalization on only one Cp ring of symmetrically 1,1′-disubstituted ferrocenes as shown in Scheme 8. These symmetrically 1,1′-disubstituted ferrocenes are easily synthesized from 1,1′-dilithioferrocene directly from ferrocene [18].

One of the most interesting products is Fc′-$SnBu_3$ which can be obtained in large amounts. Starting from 10 g of ferrocenecarbaldehyde, 13.2 g of Fc′-$SnBu_3$ (56% yield) are isolated as an essentially pure compound. This red oil can be kept at r.t. at least for several months without apparent decomposition. This compound gave us efficient and easy access to different ferrocenyl compounds as described, for example, in Scheme 9.

3. Synthesis of trisubstituted ferrocenes from ferrocenecarbaldehyde

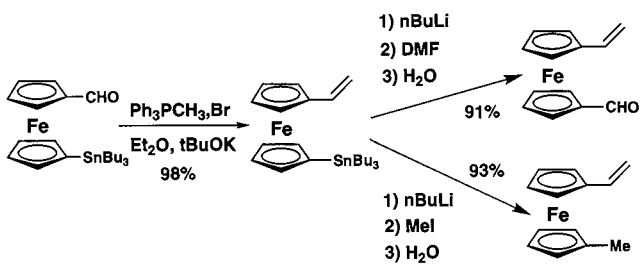
Until now, although their frequent and successful use in asymmetric catalysis, chiral trisubstituted ferrocenes have been essentially obtained by only two ways:

- The first one starts with the treatment of a chiral amine like *N*,*N*-dimethyl-1-ferrocenyl-ethylamine (**a**) first with *n*-BuLi and then with *n*-BuLi/TMEDA,

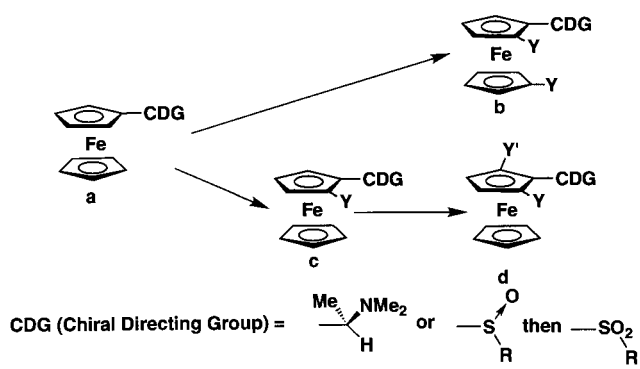


Scheme 8.

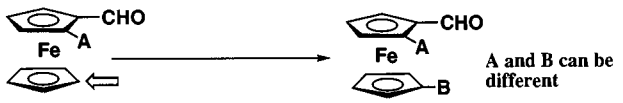
followed by an electrophilic attack to get the chiral trisubstituted compounds (**b**) with $Y = PPh_2$ [19] or SR [20] (Scheme 10). The diphosphino compounds of type (**b**) makes a very interesting family of ligands



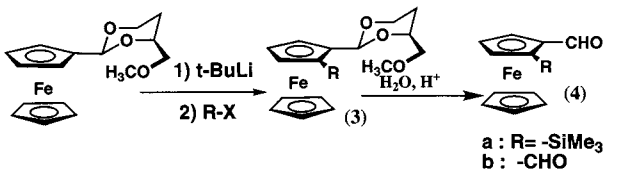
Scheme 9.

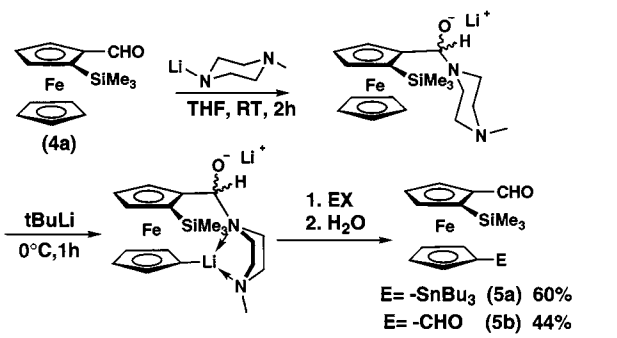


Scheme 10.



Scheme 11.





Scheme 12.

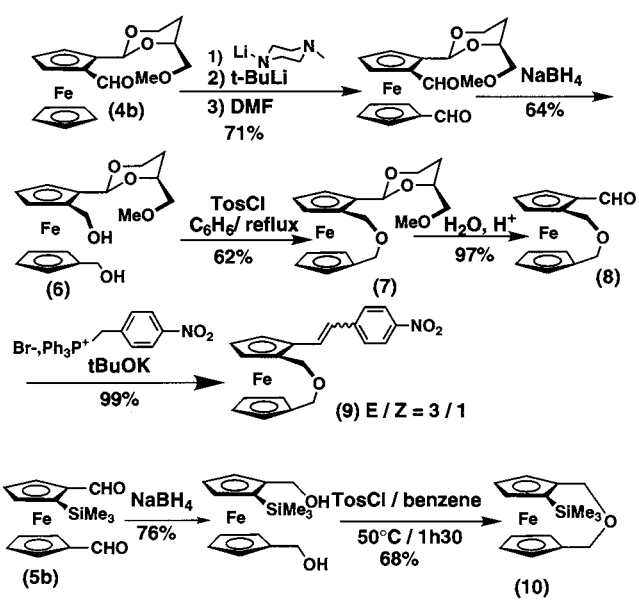
for asymmetric catalysis with often excellent efficiency (see Scheme 1) ([1], [4]a). But this method gives no way to obtain, if needed three different substituents on the ferrocene.

- The second one uses a chiral sulfoxide ([8]a) which is functionalized by a selective lithiation in one of the two positions (de > 98%). In that stage, the addition of one other equivalent of *n*-BuLi followed by an electrophilic trapping of the organolithium compound yields trisubstituted compounds of type (b) (Scheme 10). If the first lithiation is followed by the addition of an electrophile, a chiral 1,2-disubstituted ferrocenyl sulfoxides is obtained. Subsequent oxidation of this sulfoxide into a sulfone followed by its lithiation, then electrophilic trapping, gives 1,2,3-trisubstituted ferrocenes with a sulfone group in the 2-position and two different substituents (Scheme 10) ([8]a).

It seemed to us that the method of functionalization in the 1′ position described above, if applied to the recently described enantiomerically pure 1,2-disubstituted ferrocenes [7] could be an efficient way to obtain enantiomerically pure 1,2,1′-trisubstituted ferrocenes according to Scheme 11. This method seems to be compatible with a large range of A group and with an even larger range of B group.

Applying our own selective functionalization on the 1′ position to the aldehyde (**4a**) obtained by the procedure described by Kagan in 1993 [7] (see Scheme 12), we observed a very high regioselectivity in favor of the 1′ position versus the 2-position (> 98/2 established by ^{1}H-NMR on the crude product), much higher than the regioselectivity of similar reactions on ferrocenecarbaldehyde (ca. 90/10) [21]. This high selectivity is probably due to the steric hindrance of the trimethylsilyl group in the 2 position. (**5a**) is, to our knowledge, one of the very few examples of an enantiomerically pure 1,2,1′-ferrocene with three different groups [22]. Furthermore, these three substituents can react independently. So (**5a**) can be a starting point for the synthesis of various new interesting compounds according to the diversity of reactivities of the stannyl group and even more of the formyl group.

The aldehyde (**4b**) has a reactivity very similar to (**4a**) (regioselectivity up to 98/2, see Scheme 12). The aldehydes (**5a**) and (**6**) allowed us to synthesize the first chiral 1,1′-(*β-oxa*-trimethylene)ferrocenes (**7**), (**8**), (**9**) and (**10**) after reduction of the dialdehydes into the corresponding diols by sodium borohydride followed by a dehydration with tosyl chloride using a modification of the procedure described by Hillman et al. ([23]a) (see Scheme 13). Indeed some 1,1′-(*β-oxa*-trimethylene)ferrocenes were reported in the literature, but, to our knowledge, there are no examples of such chiral 1,1′-(*β-oxa*-trimethylene)ferrocenes [23]. The deprotonation of 1,1′-(*β-oxa*-trimethylene)ferrocene (**13**)



Scheme 13.

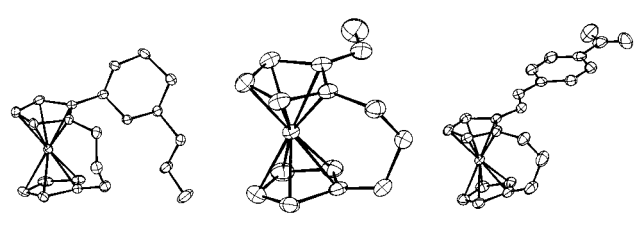
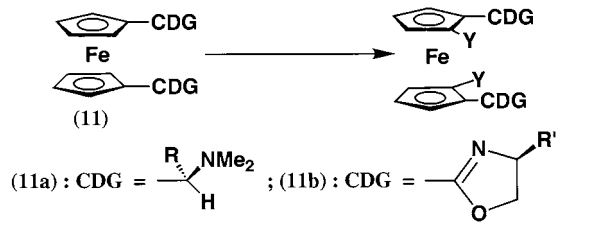
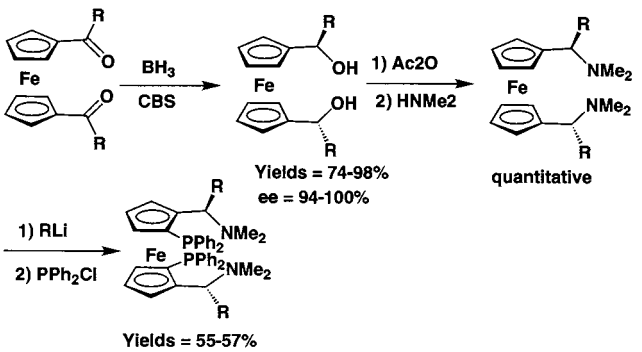


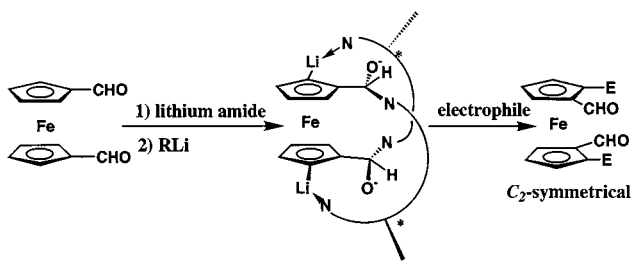
Fig. 1. CAMERON™ drawings of molecules **7**, **8** and **E**-(**9**).



Scheme 14.



Scheme 15.



Scheme 16.

was tried with *n*-BuLi/TMEDA but the ferrocenophane is totally destroyed without detection of substituted compounds in 2 or 3 position [24]. Furthermore, it is worth pointing out that, to the best of our knowledge, the only examples of synthesis of enantomerically enriched chiral ferrocenophanes are the enantioselective microbial kinetic resolution of racemic 2 and 3-formyl-[4]-ferrocenophane by bakers' yeast (ee up to 89 with 20% yield) [25] and the functionalization of Ugi's amine by dilithiation with *n*-BuLi/TMEDA then trapping of the dilithiated intermediate by tetrachlorosilane [26]. The molecule (**8**) bearing a reactive formyl group seems to be of a particular interest. For example, we used it to synthesize the interesting chromophore for Non Linear Optics **E-(9)** by a Wittig reaction followed by a fractional crystallization of the E isomer.

In addition, we were able to obtain crystal structures by X-ray diffraction of the compounds (**7**), (**8**) and **E-(9)**. Their molecular structures (CAMERON) [27] are shown in Fig. 1. The presence of a substituent on one of the ferrocene rings in 2 position with respect to the *β-oxa*-trimethylene bridge, does not seem to influence the overall geometry of the ferrocenophane framework. The bond lengths and angles in the ferrocenophane part are quite close and very similar to the unsubstituted 1,1′-(*β-oxa*-trimethylene)ferrocene.

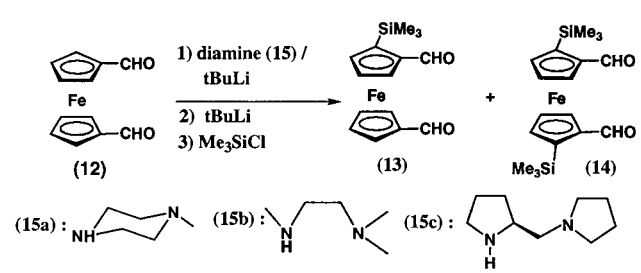
4. Synthesis of tri and tetrasubstituted ferrocenes from 1,1′-ferrocenedicarbaldehyde

Chiral tetrasubstituted C_2-symmetric ferrocene derivatives with planar chirality started only recently to receive much attention despite their attractive structures. Most of the synthesis of enantiomerically pure tetrasubstituted ferrocenes, already reported, follow the diastereoselective ortholithiation route (Scheme 14):

The first example ((**11a**), $R = CH_3$) was reported by Hayashi, Ito, Yanagi et al. in 1989 [28]. For its preparation, the starting diamine (**11a**) ($R = CH_3$) had to be used as a racemic mixture because it could not been resolved. So the tetrasubstituted ferrocene was obtained as a racemic mixture which was successfully resolved with tartaric acid. Recently, Knochel et al. described an efficient synthesis of enantiomerically pure diamines (**11a**) ($R = n\text{-}C_5H_{11}$ and C_6H_5), using, as a key step, an enantioselective borane reduction of diketone in the presence of an oxazaborolidine catalyst to yield an enantiomerically pure diol which was transformed into the diamine (**11a**) (see Scheme 15) [29].

When an oxazoline group was used as CDG (**11b**, $R = i\text{-}C_3H_7$ or $t\text{-}C_4H_9$), the stereochemistry and the rate of lithiation were very dependent upon the organolithium compounds used in the lithiation step [30]. However, good yields and good diastereoselectivities in favor of C_2-symmetric tetrasubstituted derivatives (up to 85%) was observed, when *s*-butyllithium in THF was employed ([30]b). Only very recently were reported enantioselective ortholithiation of a 1,1′-ferrocenyl diamides (direct method) [31] using *n*-BuLi/sparteine followed by an electrophilic trapping which yields a 1,2,1′-trisubstituted ferrocene (ee = 80%). After purification and enantiomeric enrichment to ee = 100%, the 1,2,1′-trisubstituted ferrocene is functionalized in the same conditions to give the 1,2,1′,2′-C_2-symmetric tetrasubstituted ferrocene with ee = ca. 90%.

These C_2-symmetric tetrasubstituted ferrocene derivatives were successfully applied to asymmetric



Scheme 17.

Table 2
Direct synthesis of chiral tri and tetrasubstituted ferrocenes from (**12**) according to Scheme 17

Entry	Conditions[a]	Diamine	Solvent	Conv.[b] (%)	(**13**) Yield (%)	(**14**) Yield (%)	Total recovered (**12**)+(**13**)+(**14**) (%)
1	−45°C/0.5 h	(**15a**)	C_6H_6/THF (1/1, v/v)	67	**47**	1	81
2	−45°C/1 h	(**15a**)	C_6H_6/THF (1/1, v/v)	78	47	6	55
3	−45°C/1 h	(**15a**)	nC_5H_{12}/THF (1/1, v/v)	64	**51**	1	88
4	−78°C/1 h	(**l5b**)	Ether	52	27	**9**	88

[a] Conditions of the deprotonation step with 2.3 equiv. of *t*-BuLi.
[b] Conversion of (**12**).

Table 3
Direct synthesis of chiral tri and tetrasubstituted ferrocenes from (**12**) according to Scheme 17

Entry	Conditions[a]	Conv.[b] (%)	(**13**) Yield (%)[c]	(**14**) Yield (%)[c]	Total recovered[c] (**12**)+(**13**)+(**14**) (%)	(**13**) ee (%)[d]	(**14**) ee (%)[e]
1	1.5 eq. *t*-BuLi/−78°C/1 h	80	**29**	0	49	**96**	—
2	1.5 eq. *t*-BuLi/−45°C/1 h	85	15	0	30	**96**	—
3	3.0 eq. *t*-BuLi/−78°C/0.5 h	77	13	23	59	78	>**99**
4	3.0 eq. *t*-BuLi/−78°C/1 h	90	25	**28**	63	60	>**99**
5	3.0 eq. *t*-BuLi/−78°C/3 h	97	19	26	48	66	**98**
6	5.0 eq. *t*-BuLi/−78°C/3 h	100	13	24	37	56	**96**

[a] 2.2 equiv. of **2**. Electrophile was $ClSiMe_3$.
[b] Conversion of (**12**).
[c] Isolated yields.
[d] (R) configuration in all cases.
[e] (R–R) configurations in all cases.

catalysis of various reactions like the cross-coupling reaction of vinyl bromide with 1-phenylethylzinc chloride (ee up to 93%) [32] or the palladium-catalyzed asymmetric allylic substitution (ee up to 99%!) [33]. Furthermore, very recently, the oxazoline groups were converted into ester groups to yield the corresponding C_2-symmetric diphosphines ligands with only the planar chirality on ferrocene. These new ligands proved to be efficient ligands for palladium-catalyzed asymmetric allylic substitution (ee up to 92%) [34].

We attempted to apply our method of functionalization in the 1′ position of ferrocenecarbaldehyde to 1,1′-ferrocenedicarbaldehyde, hoping to end up with a C_2-symmetrical product according to Scheme 16.

In order to test our idea, we started the study in racemic version with *N*-methylpiperazine (**15a**) and *N*,*N*,*N*′-trimethylethylenediamine (**15b**) (see Scheme 17). Table 2 summarizes the best results obtained after many attempts to carry out this reaction. First, it is worth pointing out that both for the monofunctionalized (**13**) and the difunctionalized (**14**) in any case, the regioselectivity is complete: only products of functionalization in a 2 position are observed. No products of overfunctionalization (with 3 or more trimethylsilyl group) were observed also. But if (**13**) can be obtained in fair yields (up to 51% isolated yield, Table 2, entry

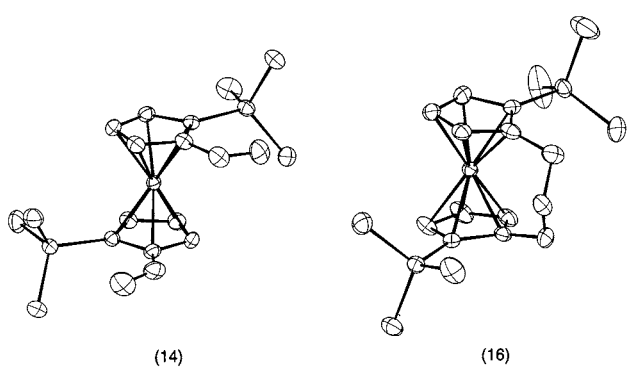
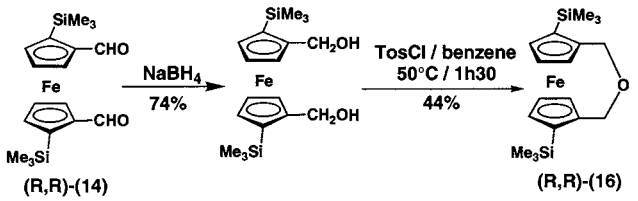


Fig. 2. CAMERON ™ drawings of molecules **14** and **16**.



Scheme 18.

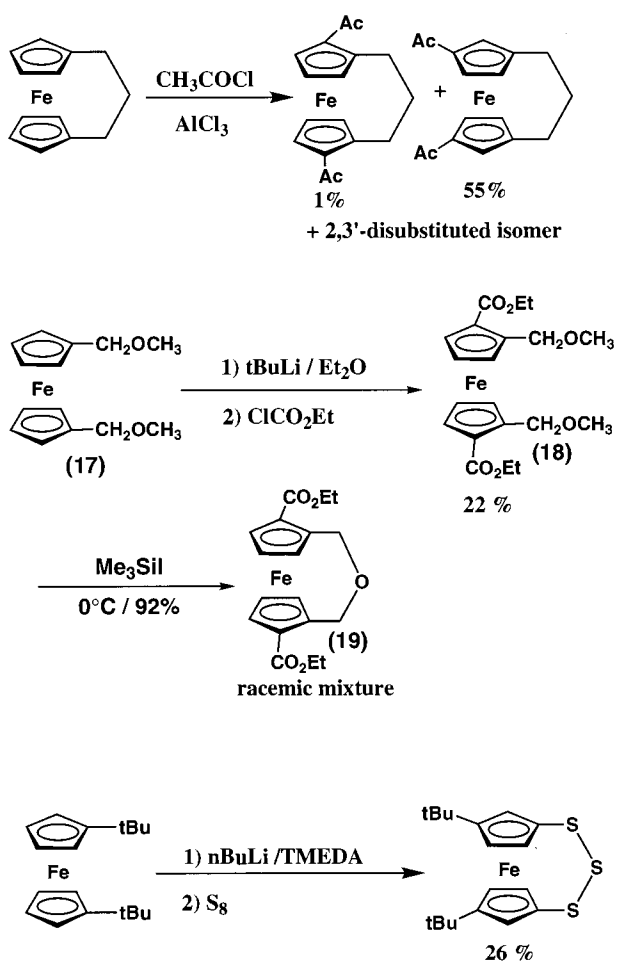
3), we could not find good conditions to synthesize the racemic (**14**) (up to only 9% isolated yield (see Table 2, entry 4), using the less hindered diamine (**15b**)).

We tried the chiral version with the commercially available diamine (**15c**). The monosilylated product (**13**) is obtained with a moderate yield (29% isolated yield after purification by flash chromatography) but a very high enantiomeric excess (96%, Table 3, entry 1) in favor of the R configuration. Once again, no other mono or disubstituted compounds could be detected but significant amounts of brown materials, insoluble in every solvent used, were observed, indicating a partial decomposition of the ferrocene derivatives in these conditions. Increasing the temperature in the deprotonation step (-45°C) decreases the yields (15%) but without loss of enantioselectivity (Table 3, entry 2). Furthermore, with an excess of *t*-BuLi, the C_2-symmetric disilylated compound (**14**) was isolated in 28% yield together with 25% of (**13**) (Table 3, entry 4). The enantiomeric excess of (**14**) is very high (>99%, the minor enantiomer can not be detected by NMR) [35]. So, amongst the ten different regio and stereisomers which can be obtained by difunctionalization of 1,1′-ferrocenedicarbaldehyde, only one compound is produced by the reaction: (**R,R**)-(**14**)! The molecular structure of (**R,R**)-(**14**) was fully characterized by X-ray crystallography as shown in Fig. 2, which confirms the double substitution in 2 and 2′ positions and the C_2-symmetry of the compound. The configurations for the planar chirality of (**14**) are R and R, as expected, because the trisubstituted compound (**13**), obtained by the reaction, have a (**R**)-planar chirality.

It is worth pointing out that with a large excess of *t*-BuLi (5 equiv., Table 3, entry 6) or longer deprotonation reaction times (Table 1, entries 5 and 6), we observed a small loss of the enantioselectivity of (**14**) (down to 96%). This decrease of enantioselectivity with an excess of *t*-BuLi is also observed for **6** but to a greater extent (down to 56%, Table 3, entry 6).

The enantiomerically pure (**14**) was transformed into (**16**) according to Scheme 18. (**R,R**)-(**16**) is, to our knowledge, the very first chiral enantiomerically pure C_2-symmetrical tetrasubstituted ferrocenophane. Fig. 2 discloses also the molecular structures (CAMERON) [27] of (**R,R**)-(**16**) obtained by X-ray diffraction.

In fact, some chiral C_2-symmetrical tetrasubstituted ferrocenophanes have already been described but always as a racemic mixture (see Scheme 19) [36–38].



Scheme 19.

5. Conclusion

The different methods described above can give a direct and efficient access to various 1,2-disubstituted, 1,2,1′-trisubstituted and 1,2,1′,2′-C_2 symmetrical tetrasubstituted ferrocenes in an enantiomeric pure form, if necessary. So we hope that such new ferrocenic structures, now more available, can be useful and will find application in many fields of chemistry, such as asymmetric catalysis, materials science, etc.

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