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Substitution of Ferrocenyl Acetates with Organozinc Reagents. An Enantioselective Preparation of Polyfunctional Chiral Ferrocenes

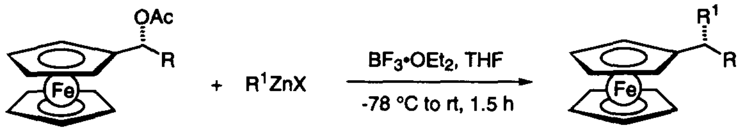
Juan J. Almena Perea, Tania Ireland and Paul Knochel*

Fachbereich Chemie der Philipps-Universität Marburg, Hans-Meerwein-Straße,
D - 35032 Marburg, Germany

Abstract: The substitution reaction of α-ferrocenyl acetates with diorganozincs or reactive organozinc halides in the presence of $BF_3 \cdot OEt_2$ in THF (-78 °C to rt, 1.5 h) provides new α-chiral ferrocenes with retention of configuration (95-100 % retention).

Chiral ferrocenes have found increasing applications as chiral ligands for transition metal catalysis.[1] There is a need for stereochemically controlled synthesis of chiral ferrocenyl precursors which may serve for the preparation of new chiral ligands. Although it is well known that substitutions at α-ferrocenyl acetates and related derivatives proceed highly stereoselectively with heteroatomic nucleophiles,[2,3] few examples are known for substitutions with *carbon* nucleophiles.[4] Recently, we have reported[3,5] a simple preparation of optically pure (> 98 % *ee*) ferrocenyl alcohols by using the Corey-Itsuno CBS-reduction.[6] Herein, we wish to describe a highly stereoselective substitution of α-ferrocenyl acetates of type **1** and **2** with various organozinc reagents **3** in the presence of $BF_3 \cdot OEt_2$ leading to chiral ferrocenes **4** and **5** in good to excellent yields and with retention of configuration[7] (> 95 % retention in most cases) (Scheme 1; Table 1 and 2).

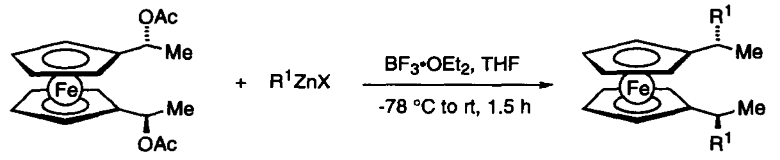
Scheme 1



1a : R = Ph; 97 % *ee*
1b : R = Me; 98 % *ee*

3 : X = R^1 or Halide

4a-m : 64-98 % yield; 92-98 % *ee*



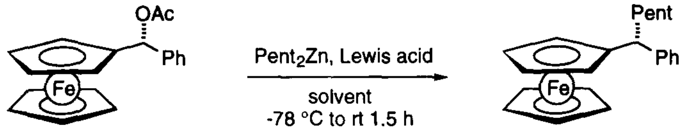
2 : 98 % *ee*

3 : X = R^1 or Halide

5a-d : 61-96 % yield; 94-98 % *ee*

A preliminary study performed with the ferrocenyl acetate **1a** (97 % *ee*) and $Pent_2Zn$ showed that among the Lewis acid tested ($ZnBr_2$, LiCl and $BF_3 \cdot OEt_2$), $BF_3 \cdot OEt_2$ provided the highest yields and the best stereoselectivities (up to 97 % *ee*) using THF as solvent. With diethyl ether or acetonitrile lower stereoselectivities were obtained (73-83 % *ee*; see Table 1).

Scheme 2



1a : 97 % *ee*

4a : up to 98 % yield and 97 % *ee*

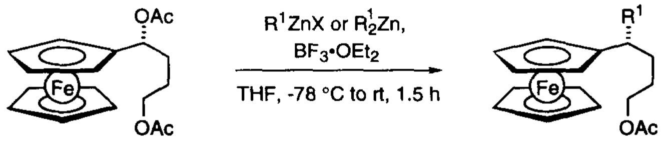
Table 1. Optimization of the addition of $Pent_2Zn$ to the ferrocenyl acetate **1a**.

Lewis acid	solvent	yield (%)[a]	*ee* (%)[b]
--	THF	68	94
$ZnBr_2$	THF	71	89
LiCl	THF	88	85
$BF_3{\cdot}OEt_2$	THF	98	97
$BF_3{\cdot}OEt_2$	ether	68	73
$BF_3{\cdot}OEt_2$	MeCN	96	96

[a] Isolated yield of analytically pure product. [b] Determined by HPLC (Chiralcel OD)

Interestingly, this substitution can be extended to a variety of organozinc derivatives (Table 2). Best results are obtained with diorganozincs ($R^1{}_2Zn$; entries 1, 4, 7 and 9 of Table 2) or reactive organozinc halides like allylzinc bromide[8] (entries 2 and 5), a benzylic zinc bromide[9] (entry 6), an alkenylzinc bromide[10] (entry 8) or a secondary alkylzinc iodide[11] (entry 3). For the transfer of primary alkyl groups, it was noticed that reagents of the type RZnI furnish substituted ferrocenes with low enantioselectivity,[12] due to their moderate reactivity. Remarkably, allylzinc bromide does not attack the carbonyl of the acetate function but undergoes only the substitution reaction, confirming the role of $BF_3{\cdot}OEt_2$ to the generation of a configurationally stable but highly reactive α-ferrocenyl cation which is rapidly trapped by the zinc organometallic.[2] This substitution reaction proceeds also well with functionalized ferrocenyl acetates. Thus, the diacetate **1c** (97 % *ee*) reacts with Me_2Zn, *i*-Pr_2Zn[13] or allylzinc bromide[8] in good yields giving the functionalized ferrocenes **4k-m** with > 94 % *ee* (Scheme 3).

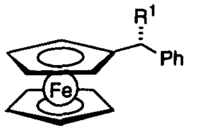
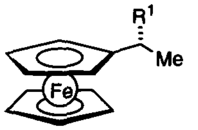
Scheme 3



1c : 97 % *ee*

4k : R^1 = Me; 78 % yield; 94 % *ee*
4l : R^1 = *i*-Pr; 85 % yield; 97 % *ee*
4m : R^1 = allyl; 92 % yield; 95 % *ee*

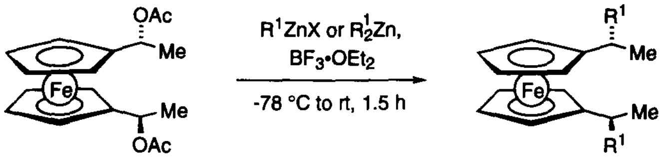
Table 2. Chiral ferrocenes of type **4** obtained by the reaction of the ferrocenyl acetates **1a-b** with organozinc reagents in the presence of $BF_3 \cdot OEt_2$.

entry	ferrocene **1a-b**	zinc reagent of type **3**	ferrocene of type **4**	yield (%)[a]	*ee* (%)[b]	α_D (*c*)[c]
						
1	**1a**	$(Me_3SiCH_2)_2Zn$	**4b**: $R^1 = CH_2SiMe_3$	90	94	+74.0 (1.30)
2	**1a**	allylzinc bromide	**4c**: R^1 = allyl	96	95	+68.4 (1.21)
3	**1a**	*i*-PrZnI	**4d**: R^1 = *i*-Pr	98	95	+116.1 (1.10)
						
4	**1b**	$(Me_3SiCH_2)_2Zn$	**4e**: $R^1 = CH_2SiMe_3$	92	97	-7.6 (2.50)
5	**1b**	allylzinc bromide	**4f**: R^1 = allyl	87	98	+2.5 (1.51)
6	**1b**	*m*-$MeC_6H_4CH_2ZnBr$	**4g**: $R^1 = CH_2C_6H_4$(*m*-Me)	64	98	+5.4 (1.10)
7	**1b**	$(AcO(CH_2)_4)_2Zn$	**4h**: $R^1 = (CH_2)_4OAc$	70	98	+2.9 (1.09)
8	**1b**	(*E*)-PhCH=CHZnBr	**4i**: R^1 = (*E*)-CH=CH-Ph	78	92	-110.3 (1.00)
9	**1b**	Ph_2Zn	**4j**: R^1 = Ph	70	97	-98.0 (1.13)

[a] Isolated yield of analytically pure product. [b] Determined by HPLC (Chiralcel OD or OJ). [c] α_D was measured in $CHCl_3$.

Finally, the use of α-ferrocenyl diacetate **2** derived from C_2 symmetrical ferrocenyl diol[3] (98 % *ee*) provides as expected new C_2-symmetrical ferrocenes[14,15,16] of type **5** with high stereoselectivities (94-98 % *ee*; Scheme 4).

Scheme 4



2 : 98 % *ee*

5a : R^1 = Ph; 78 % yield; 94 % *ee*
5b : $R^1 = CH_2SiMe_3$ yield; 85 %; 97 % *ee*
5c : R^1 = (*E*)-CH=CH-Ph; 61 % yield; 98 % *ee*
5d : R^1 = allyl; 96 % yield; 98 % *ee*

In summary, we have prepared a range of new chiral ferrocenes using a new substitution of ferrocenyl acetates with diorganozincs and organozinc halides. Applications toward the preparation of new ferrocenes containing chiral ligands are underway.

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12. The substitution of **1a** with $AcO(CH_2)_4ZnI$ afforded the corresponding substituted ferrocene with 20 % *ee*. The use of $AcO(CH_2)_4Cu(CN)ZnI$ improves the stereoselectivity to 41 % *ee*.
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14. These ferrocenes contain between 1-5 % of *meso*-compound.
15. **Typical procedure.** *Typical procedure for the reaction of the acetate* **1a** *with dipentylzinc.* To a solution of compound **1a** (100 mg, 0.3 mmol) in dry THF (5 mL) at -78 °C under argon was added dipentylzinc (0.09 mL, 0.45 mmol) and $BF_3{\cdot}OEt_2$ (0.04 mL, 0.3 mmol). The reaction mixture was allowed to warm to rt for 1.5 h. After an additional 1 h of stirring, the reaction mixture was worked up as usual. The crude product was purified by column chromatography (hexanes / *t*-BuOMe: 30 / 1) affording pure product **4a** as an orange oil (102 mg, 98 % yield; $\alpha_D = +71.0$ ($c = 1.05$, $CHCl_3$); 97 % *ee* determined by HPLC using a Chiracel OD column with a flow rate of 0.6 mL / min, *n*-heptane with 1 % of isopropanol as eluent and detection at 254 nm).
16. Optical rotation values for compounds **4k-m** and **5a-d** follow: **4k**: $\alpha_D = +1.3$ ($c = 1.26$, $CHCl_3$); **4l**: $\alpha_D = +63.8$ ($c = 1.67$, $CHCl_3$); **4m**: $\alpha_D = -7.9$ ($c = 1.22$, $CHCl_3$); **5a**: $\alpha_D = -148.0$ ($c = 1.03$, $CHCl_3$); **5b**: $\alpha_D = -10.6$ (c = 1.15, $CHCl_3$); **5c**: $\alpha_D = -167.3$ ($c = 0.52$, $CHCl_3$); **5d**: $\alpha_D = +11.6$ ($c = 1.90$, $CHCl_3$).

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