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Stereoselective substitution of α-aminoalkylferrocenes with diorganozincs. A fast synthesis of new chiral FERRIPHOS ligands for asymmetric catalysis

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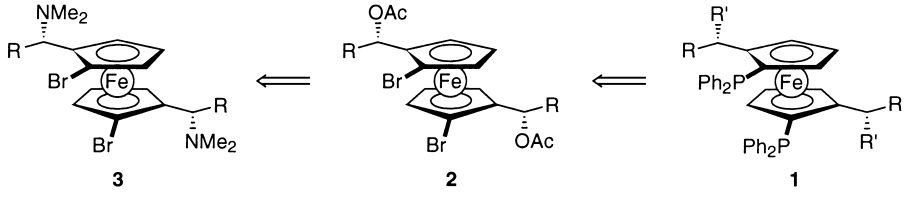
Abstract

A direct stereoselective substitution of α-aminoalkylferrocenes of type **3** with organozinc reagents provides chiral ferrocenes which can be converted to the FERRIPHOS ligands of type **1** in a one-pot procedure. These FERRIPHOS ligands have been used for the Rh-catalyzed asymmetric hydrogenation of an enol acetate with 94.9% *ee*.

Chiral ferrocenylphosphines are important ligands for asymmetric catalysis.[1] Recently, we have reported a new class of such ligands: the FERRIPHOS ligands of type **1**[2–4] (Scheme 1). These diphosphines proved to be very efficient for the asymmetric hydrogenation of α-acetamidoacrylic acid derivatives affording high enantioselectivities (>97% *ee*).[2]



Scheme 1.

The preparation of the ligands **1** required the synthesis of the sensitive diacetoxyferrocene derivatives of type **2** which were obtained from the stable and easy to handle diaminoferrocene derivatives of type **3**. We have examined the direct substitution of the dimethylamino groups of **3** with diorganozincs since it would avoid the synthesis and handling of the diacetates **2**. Herein, we wish to report the successful direct stereoselective substitution reaction as well as some new applications of the FERRIPHOS catalysts for the asymmetric reduction of enol acetates. A recent publication by Salzer et al. has shown that benzylic

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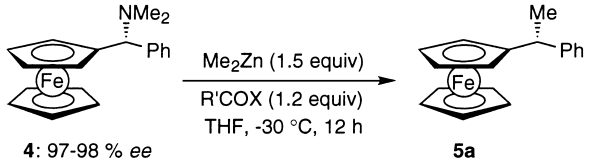
dimethylaminochromium complexes undergo enantiospecific nucleophilic substitutions with chloride ions[5] using ethyl chloroformate to activate the dimethylamino group. In preliminary experiments, we have examined the substitution of the monodimethylaminoferrocene derivative **4** (97–98% *ee*) with organozinc reagents in the presence of various acid chlorides (Table 1). We found that a range of acylating agents were efficient for this nucleophilic substitution with dimethylzinc (THF, −30°C, 12 h). The stereoselectivity of the reaction was optimal using acetyl chloride leading to the substitution product **5a** with 96.5% *ee* (ca. 98% retention of configuration; entry 2 of Table 1).

Table 1
Nucleophilic substitution of the dimethylaminoferrocene derivative **4** with Me_2Zn and an acylating agent

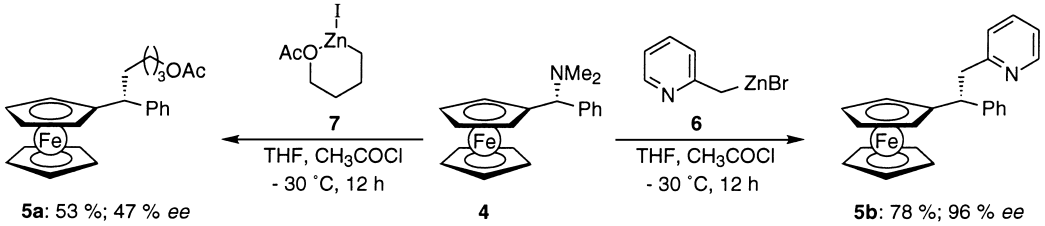


4: 97-98 % *ee* **5a**

Entry	R'COX	yield (%)[a]	(%)*ee* [b]
1	$ClCO_2Et$	95	95
2	CH_3COCl	97	96.5
3	PhCOCl	95	94
4	$(CF_3CO)_2O$	95	93.5

[a]Isolated yield of analytically pure product. [b]Enantioselectivity determined by HPLC. A Chiralcel OD column (Daicel Chemical Industries) was used at 30 °C with n-heptane / 2-propanol 9:1 as mobile phase; flow 0.6 mL/min; detection by diode array uv-vis detector at 254 nm.

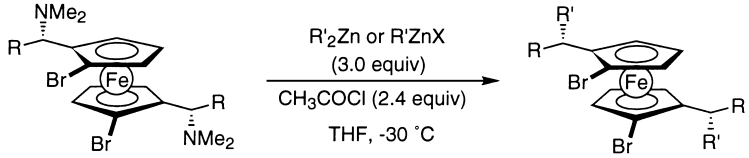
Under these conditions, reactive organozinc halides like 2-picolylzinc bromide **6** prepared by the lithiation of 2-picoline followed by a transmetallation with zinc bromide[6] undergo a smooth substitution with ca. 98% retention of configuration. However, unreactive organozinc halides like 4-acetoxybutylzinc iodide[7] **7** furnish a moderate yield and low enantioselectivity (47% *ee*; see Scheme 2). This can be explained by the generation of the configurationally unstable α-ferrocenyl carbocation. Next, we examined the substitution with the FERRIPHOS precursors of type **3** (R=Ph, Me) and were pleased to find that the double substitution occurs with complete retention of configuration furnishing the expected chiral ferrocene derivatives **8** (see Table 2). The ferrocenes **3a–b** were converted in a one-pot procedure to the desired FERRIPHOS ligands **1a–b**.



5a: 53 %; 47 % *ee* **5b**: 78 %; 96 % *ee*

Scheme 2.

Table 2
C_2-symmetrical ferrocene derivatives **8a–d** obtained by the stereoselective substitution of the aminoferrocenes **3a–b** with organozinc reagents in the presence of CH_3COCl



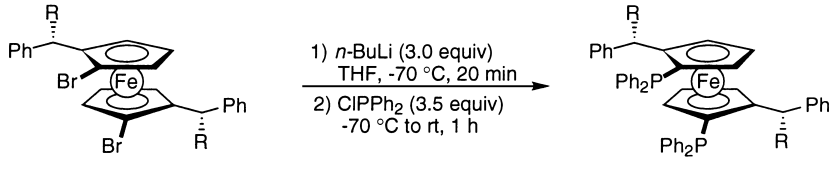
3a : R = Ph
3b : R = Me

8a : R = Ph; R' = *i*-Pr
8b : R = Ph; R' = Me
8c : R = Ph; R' = allyl
8d : R = Me; R' = allyl

Entry	Substrate	Zinc reagent	Product of type **8**	Yield (%)[a]	(%)*ee* [b]
1	**3a**	*i*-Pr$_2$Zn	**8a**	76	> 99
2	**3a**	Me$_2$Zn	**8b**	79	> 99
3	**3a**	allylzinc bromide	**8c**	96	> 99[c]
4	**3b**	allylzinc bromide	**8d**	86	> 99[c]

[a]Isolated yield of analytically pure product. [b]Enantioselectivity determined by HPLC. A Chiraldex OD Column (Daicel Chemical Industries) was used at 30 °C with n-heptane / 2-propanol 9:1 as mobile phase; flow 0.6 mL/min; detection by diode array uv-vis detector at 254 nm. [c]Enantioselectivity determined by HPLC (under the conditions described above) after hydroboration of the dialkene with Et_2BH and oxidation to the corresponding terminal diol.

Thus, the treatment of **3a–b** with *n*-BuLi (3.0 equiv., THF, −70°C, 20 min) furnishes the corresponding lithiated intermediates which by the reaction with $ClPPh_2$ (3.5 equiv., −70°C to rt, 1 h) provide the FERRIPHOS **1a** (42%) and **1b** (50%) in enantiomerically pure form (>99% *ee*) (Scheme 3).



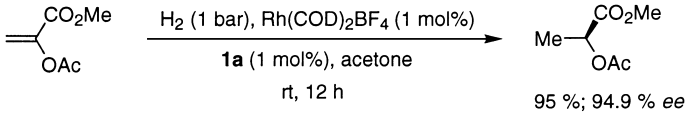
8a: R = *i*-Pr
8b: R = Me

1a: R = *i*-Pr; 42 %
1b: R = Me; 50 %

Scheme 3.

The catalytic activity of the new FERRIPHOS ligands was tested in the rhodium catalyzed asymmetric reduction of the enol acetate **9**.[8a,8b] A smooth hydrogenation took place [1 bar H_2, $Rh(COD)_2BF_4$ (1 mol%), acetone, **1a** (1 mol%); 25°C, 12 h] providing the 2-acetoxyester **10** in 95% yield and 94.9% *ee* (Scheme 4). Interestingly, the ligand of type **1** bearing dimethylamino groups (R=NMe_2) was not a catalyst for this reaction.[9]

In summary, we have developed a direct substitution[10] of aminoferrocene derivatives with organozinc reagents allowing a more straightforward synthesis of FERRIPHOS ligands. We have also demonstrated the utility of these new diphosphines for the asymmetric reduction of an enol acetate.



Scheme 4.

Acknowledgements

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9. Unpublished results
10. Typical procedure: In a 50 mL flask equipped with an argon-inlet, the ferrocenyl diamine **3a** (500 mg, 0.83 mmol) was dissolved in THF (20 mL) under argon and cooled to −30°C. Via a syringe Zn(*i*-Pr)$_2$ (1.47 M in THF, 1.67 mL, 2.46 mmol) and acetyl chloride (0.14 mL, 1.97 mmol) was added in this order. The reaction mixture was allowed to warm to room temperature overnight. After aqueous work-up and extraction with *t*-butyl methyl ether, the combined organic layers were dried ($MgSO_4$), filtrated and the solvent was evaporated under reduced pressure. The crude product was purified by filtration over silica gel (*n*-pentane) affording compound **8a** [379 mg, 0.62 mmol, 76% yield, >99% *ee*; HPLC: OD, 0.5% *i*-PrOH, 0.6 mL/min, 215 nm, t_R/min=6.81 (*RR*), 8.09 (*SS*)].