# Synthesis of versatile intermediates of the ferrocene series: reductive amination of ferrocenecarbaldehyde

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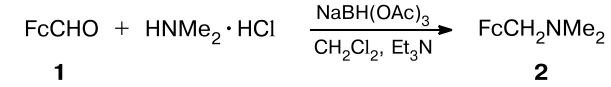
Reductive amination of ferrocenecarbaldehyde with several primary and secondary amines in the presence of sodium triacetoxyborohydride was studied. This method was used for the synthesis of new ferrocenylmethylamines, *viz.*, *N*-(ferrocenylmethyl)isoleucine methyl ester, *N*,*N*-bis(ferrocenylmethyl)glycine ethyl ester, and *N*-(3,5-dibenzyloxybenzyl)-*N*-(ferrocenylmethyl)methylamine. The latter is a potential precursor of a dendrimer with the chiral ferrocenyl plane in the core.

**Key words:** reductive amination, ferrocenecarbaldehyde, sodium triacetoxyborohydride, amines, dendrimers.

Reductive amination of aldehydes and ketones with sodium triacetoxyborohydride is often used in organic synthesis and allows one to prepare alkylated amines under mild conditions in high yields.[1] However, to our knowledge, the use of this reaction for the synthesis of organometallic amines, in particular, (ferrocenylmethyl)amines, is not documented. The latter compounds attract interest as important intermediates in the ferrocene synthesis due to their coordination ability, which enables one to perform regio- and sometimes stereoselective introduction of a second substituent into ferrocene. At the same time, dimethylaminomethylferrocene is one of the most popular building blocks. In our study on the use of reductive amination in the ferrocene series, we synthesized this well known compound as the first example (Scheme 1).

**Scheme 1**



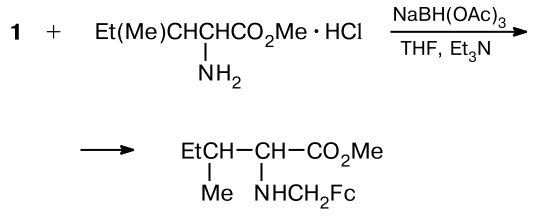

**1** **2**

Fc = $C_5H_5FeC_5H_4$

The reaction of ferrocenecarbaldehyde (**1**) with dimethylamine hydrochloride and sodium triacetoxyborohydride in the presence of triethylamine in dichloromethane afforded amine **2** as the only product (yield >90%).

Reductive amination of ferrocenecarbaldehyde with primary amines, *viz.*, derivatives of amino acids, such as glycine, L-isoleucine, and L-lysine esters, could give rise to both secondary amines (the reaction products with one molecule of the aldehyde) and tertiary amines (due to the repeated reaction with the aldehyde). Reductive amination of aldehyde **1** with L-isoleucine methyl ester afforded exclusively monoalkylated product **3** (Scheme 2).

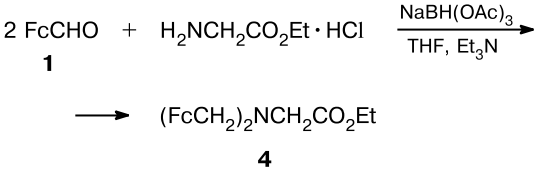
**Scheme 2**




**3**

The high yield of this compound (~92% after chromatographic purification) suggests the virtually complete absence of the repeated reaction. Reductive amination of aldehyde **1** with glycine ethyl ester proceeded differently to give tertiary amine **4** as the major reaction product (Scheme 3).

**Scheme 3**




**1** **4**

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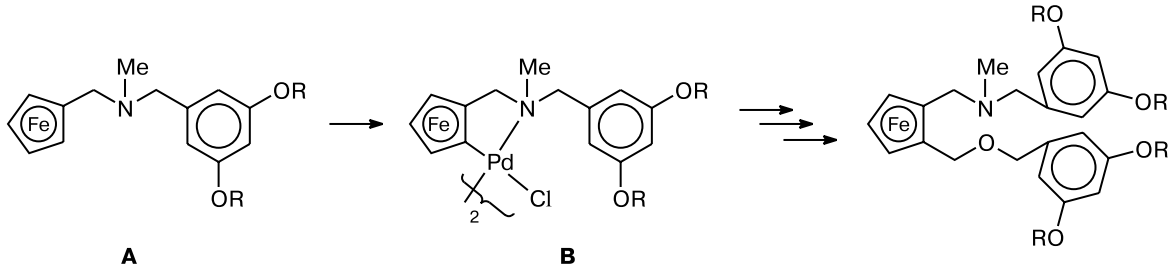
**Scheme 4**

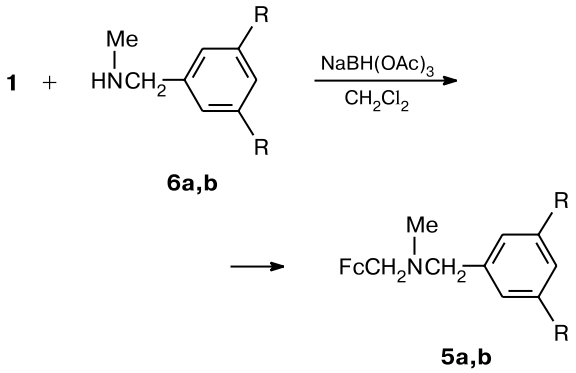



According to the published data,[1] this result is not unexpected for the reaction of an aldehyde with primary amines (in particular, with amino acid esters). The use of a ~10% excess of primary amine in reductive amination often suppresses the reaction of the secondary amine that formed with the aldehyde. However, in the case under consideration, an excess of glycine ester did not prevent the formation of compound **4**. This can be attributable to an insufficient amount of the free amine in the reaction mixture because of its slow elimination from the salt under the reaction conditions. On the other hand, it is not inconceivable that the replacement of one hydrogen atom at the nitrogen atom in glycine with the electron-donating ferrocenylmethyl group increases the basicity of the secondary amine to an extent that it becomes more reactive than the primary amine.

The reaction of L-lysine was performed with the use of 2 equiv. of aldehyde **1** with an idea to achieve complete alkylation of both amino groups. Unfortunately, this reaction gave ferrocenylmethanol as the only identified product.

Our investigation on reductive amination of ferrocenecarbaldehyde is aimed at the synthesis of the optically active core of a dendrimer containing planar-chiral disubstituted ferrocene. We intend to construct such a compound using well known and studied asymmetric cyclopalladation of appropriate (ferrocenylmethyl)amines.[2] Amine (**A**) containing a fragment of Fréchet's dendron[3] seems to be the most convenient precursor (Scheme 4).

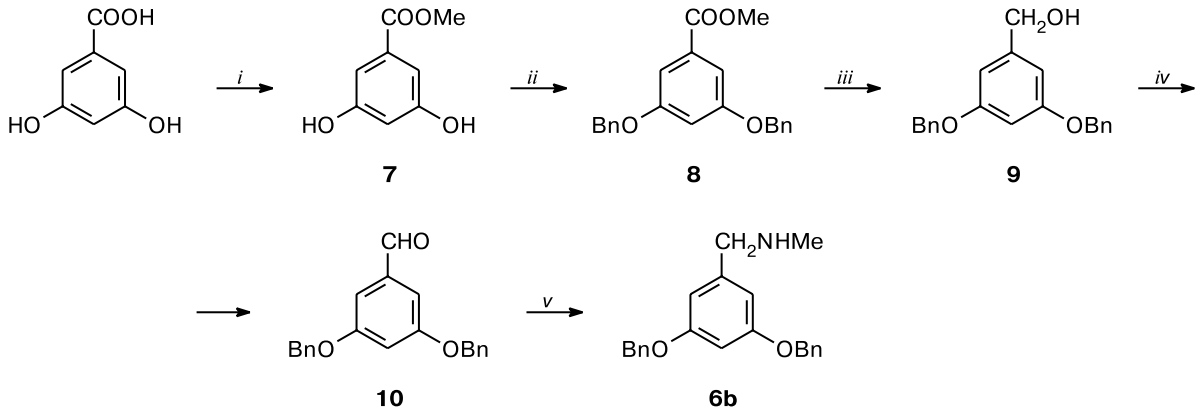
**Scheme 5**




R = H (**a**), OBn (**b**)

We chose amine **A** as the starting compound primarily because it can be synthesized from commercially available and relatively inexpensive 3,5-dihydroxybenzoic acid. The further replacement of the Pd atom in the ferrocene moiety of intermediate **B** leads to the introduction of one

**Scheme 6**




**Reagents:** *i*. MeOH, $H_2SO_4$, Δ; *ii*. BnCl, $K_2CO_3$, MeCOMe; *iii*. $LiAlH_4$, THF; *iv*. $MnO_2$, $CHCl_3$; *v*. $MeNH_2 \cdot HCl$, $NaBH(OAc)_3$, $Et_3N$, $CH_2Cl_2$.

more 3,5-dihydroxybenzyl fragment into the molecule. The drawback of this approach is possible competitive cyclopalladation at the benzene ring.

To examine the possibility of the synthesis of the required starting (ferrocenylmethyl)amine by reductive amination, we stuided this process using the synthesis of known[4] model compound **5a** as an example (Scheme 5).

Reductive amination of ferrocenecarbaldehyde **1** with benzylmethylamine **6a** was carried out under standard conditions to give the target product in high yield.

The required amine **6b** was synthesized according to Scheme 6.

Compounds **9** and **10** serve as important synthons in numerous syntheses of Fréchet's dendrimers described in the literature. Various procedures for their synthesis are available. We developed a new procedure for the synthesis of these compounds.

Reductive amination of aldehyde **1** with amine **6b** afforded secondary amine **5b**, which is the starting compound for the further synthesis of a dendrimer based on planar-chiral ferrocene.

## Experimental

The $^1$H NMR spectra were recorded on a Bruker AMX-400-ST instrument. Ferrocenecarbaldehyde[5] and $MnO_2$[6] were synthesized according to known procedures. Analytical data for dimethylaminomethylferrocene **2** are in complete agreement with the parameters of the commercial reagent (Aldrich). The melting point of methyl 3,5-dihydroxybenzoate **7** is identical to m.p. of the commercially available compound (Lancaster).

***N*-(Ferrocenylmethyl)isoleucine methyl ester (3).** Isoleucine methyl ester hydrochloride (2 g, 0.011 mol) and $Et_3N$ (1.6 mL, 0.011 mol) were added to a stirred solution of aldehyde **1** (2.14 g 0.01 mol) in THF (50 mL) and then $NaBH(OAc)_3$ (5.3 g, 0.025 mol) was added portionwise. The reaction mixture was stirred for 4 h, poured onto ice, alkalified with 10 *M* NaOH to pH 12, extracted with diethyl ether, and dried with $Na_2SO_4$. The solvent was evaporated and the residue was chromatographed on $SiO_2$ ($CHCl_3$—MeOH, 100 : 1—98 : 2). Ester **3** was obtained as an orange oil in a yield of 3.15 g (91.8%). Found (%): C, 63.21; H, 7.45; Fe, 16.36. $C_{18}H_{25}FeNO_2$. Calculated (%): C, 62.99; H, 7.34; Fe, 16.27. $^1$H NMR ($CDCl_3$), δ: 0.92 (m, 6 H, 2 Me); 1.21 and 1.57 (both m, 1 H each, $CH_2$); 1.70 (m, 2 H, CH and NH); 3.17 (d, 1 H, CH, $J$ = 6.3 Hz); 3.36 and 3.47 (both d, 1 H each, $CH_2$, $J$ = 12.7 Hz); 3.74 (s, 3 H, MeO); 4.10 (m, 2 H, $C_5H_4$); 4.16 (m, 6 H, $C_5H_4$ and $C_5H_5$); 4.24 (m, 1 H, $C_5H_4$).

***N*,*N*-Bis(ferrocenylmethyl)glycine ethyl ester (4)** was prepared analogously in 64% yield as orange crystals, m.p. 76—78 °C (hexane). Found (%): C, 62.57; H, 5.81; N, 2.85. $C_{26}H_{29}Fe_2NO_2$. Calculated (%): C, 62.56; H, 5.86; N, 2.81. $^1$H NMR ($CDCl_3$), δ: 1.27 (m, 3 H, Me); 3.16 (s, 2 H, $CH_2N$); 3.60 (s, 4 H, 2 $CH_2N$); 4.06—4.21 (m, 20 H, 2 $C_5H_4$, 2 $C_5H_5$ and $OCH_2$).

***N*-Benzyl-*N*-(ferrocenylmethyl)methylamine (5a).** Under the above-described conditions (in $CH_2Cl_2$ in the absence of $Et_3N$), compound **5a** was prepared in 92% yield as orange crystals, m.p. 37—39 °C. Found (%): C, 70.56; H, 6.45; N, 4.25. $C_{19}H_{21}FeN \cdot 0.1\ H_2CO_3$. Calculated (%): C, 70.47; H, 6.60; N, 4.30. $^1$H NMR ($C_6D_6$), δ: 2.18 (s, 3 H, Me); 3.42 and 3.49 (both s, 2 H each, $CH_2$); 4.00 (s, 5 H, $C_5H_5$); 4.04 and 4.16 (both m, 2 H each, $C_5H_4$); 7.18 (m, 1 H, Ph); 7.29 and 7.47 (both m, 2 H each, Ph).

***N*-(3,5-Dibenzyloxybenzyl)-*N*-(ferrocenylmethyl)methylamine (5b).** Sodium triacetoxyborohydride (15.26 g, 0.072 mol) was added portionwise to a stirred solution of amine **6b** (8 g, 0.024 mol) and aldehyde **1** (5.14 g, 0.024 mol) in $CH_2Cl_2$ (150 mL). The reaction mixture was stirred for 6 h, poured onto ice, alkalified with 10 *M* NaOH to pH 12, extracted with $CHCl_3$, and dried with $Na_2SO_4$. The solvent was evaporated and the residue was chromatographed on $SiO_2$ ($CHCl_3$—MeOH, 100 : 1—80 : 20). Compound **5b** was obtained in a yield of 8 g (63%) as orange crystals, m.p. 67—70 °C (hexane—AcOEt, 4 : 1). Found (%): C, 74.79; H, 5.86; N, 2.59. $C_{33}H_{33}FeNO_2$. Calculated (%): C, 74.58; H, 6.26; N, 2.64. $^1$H NMR ($CDCl_3$), δ: 2.17 (s, 3 H, Me); 3.40 and 3.44 (both s, 2 H each, $CH_2$); 4.11 (s, 5 H, $C_5H_5$); 4.13 and 4.17 (both m, 2 H each, $C_5H_4$); 5.05 (s, 4 H, 2 $CH_2$); 6.55 (s, 1 H, $C_6H_3$); 6.62 (s, 2 H, $C_6H_3$); 7.34—7.46 (m, 10 H, 2 Ph).

**Methyl 3,5-dihydroxybenzoate (7).** Sulfuric acid (2 mL) was added to a solution of 3,5-dihydroxybenzoic acid (10 g, 0.064 mol) in MeOH (70 mL). The reaction mixture was refluxed for 10 h and concentrated. The residue was dissolved in water, extracted with a 1 : 1 $CHCl_3$—$Bu^tOH$ mixture, and dried with $Na_2SO_4$. The solvent was evaporated and the residue was crystallized from water. Ester **7** (8.9 g, 82%) was obtained as colorless crystals, m.p. 164—166 °C. $^1$H NMR ($CD_3OD$), δ: 4.07 (s, 3 H, Me); 6.67 (s, 1 H, $C_6H_3$); 6.91 (s, 2 H, $C_6H_3$).

**Methyl 3,5-dibenzyloxybenzoate (8).** A mixture of ester **7** (20 g, 0.12 mol), BnCl (29.2 mL, 0.25 mol), and $K_2CO_3$ (18.4 g 0.13 mol) in $Me_2CO$ (100 mL) was refluxed with stirring for 5 days, diluted with water, extracted with $CHCl_3$, washed with water and brine, and dried with $Na_2SO_4$. The solvent was evaporated and the residue was chromatographed on $SiO_2$ ($CHCl_3$—MeOH, 100 : 1—98 : 2). Ester **8** was obtained in a yield of 37 g (93%) as colorless crystals, m.p. 68—69 °C (*cf.* lit. data[7]: m.p. 69—71 °C). $^1$H NMR ($CDCl_3$), δ: 3.93 (s, 3 H, Me); 5.09 (s, 4 H, 2 $CH_2$); 6.82 (s, 1 H, $C_6H_3$); 7.29—7.49 (m, 12 H, $C_6H_3$ and 2 Ph).

**3,5-Dibenzyloxybenzyl alcohol (9).** A solution of ester **8** (37 g, 0.111 mol) in anhydrous THF (200 mL) was added dropwise to a suspension of $LiAlH_4$ (2.1 g, 0.055 mol) in anhydrous THF (200 mL) at 5 °C. The reaction mixture was allowed to warm, stirred for 6 h, and cooled with ice. Water (5 mL) was added dropwise and then 5% $H_2SO_4$ (100 mL) was added. The mixture was extracted with diethyl ether and the extract was dried with $Na_2SO_4$. The solvent was evaporated and the residue was crystallized from $CCl_4$. Alcohol **9** was obtained in a yield of 27 g (80%) as colorless crystals, m.p. 78—80 °C (*cf.* lit. data[7]: m.p. 78—80 °C). $^1$H NMR ($CDCl_3$), δ: 4.65 (s, 2 H, $CH_2$); 5.05 (s, 4 H, 2 $CH_2$); 6.57 (s, 1 H, $C_6H_3$); 6.65 (s, 2 H, $C_6H_3$); 7.32—7.49 (m, 10 H, 2 Ph).

**3,5-Dibenzyloxybenzaldehyde (10).** Manganese oxide (11.4 g 0.131 mol) was added to a solution of alcohol **9** (20 g, 0.065 mol) in $CHCl_3$ (400 mL). The reaction mixture was stirred for 5 days, $MnO_2$ being added portionwise (10 g per day; a total amount

was ~51 g, 0.58 mol). The precipitate was filtered off and washed with $CHCl_3$. The solvent was evaporated and the residue was crystallized from a 1 : 4 hexane—AcOEt mixture. Aldehyde **10** was obtained in a yield of 15 g (75%) as colorless crystals, m.p. 78—79 °C (hexane—AcOEt, 1 : 4) (*cf.* lit. data[7]: m.p. 80.5—81 °C). $^1$H NMR ($CDCl_3$), δ: 5.00 (s, 4 H, 2 $CH_2$); 6.88 (s, 1 H, $C_6H_3$); 7.14 (s, 2 H, $C_6H_3$); 7.30—7.49 (m, 10 H, 2 Ph); 9.91 (s, 1 H, CHO).

***N*-(3,5-Dibenzyloxybenzyl)-*N*-methylamine (6b).** Methylamine hydrochloride (8.9 g, 0.132 mol) and $Et_3N$ (18.4 mL, 0.132 mol) were added to a stirred solution of aldehyde **10** (8 g, 0.026 mol) in $CH_2Cl_2$ (100 mL) and then $NaBH(OAc)_3$ (16.7 g, 0.079 mol) was added portionwise. The reaction mixture was stirred for 6 h, poured onto ice, alkalified with 10 *M* NaOH to pH 12, and extracted with $CHCl_3$. The extract was dried with $Na_2SO_4$, the solvent was evaporated, and the residue was chromatographed on $SiO_2$ ($CHCl_3$—MeOH, 100 : 1—80 : 20). Amine **6b** was obtained in a yield of 8 g (91%) as a colorless oil. Found (%): C, 77.56; H, 6.89; N, 4.10. $C_{22}H_{23}NO_2 \cdot 0.15\ H_2CO_3$. Calculated (%): C, 77.62; H, 6.85; N, 4.09. $^1$H NMR ($CDCl_3$), δ: 2.46 (s, 3 H, Me); 3.73 (s, 2 H, $CH_2$); 5.05 (s, 4 H, 2 $CH_2$); 6.55 (s, 1 H, $C_6H_3$); 6.64 (s, 2 H, $C_6H_3$); 7.30—7.49 (m, 10 H, 2 Ph).

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