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A Practical Three-Step Synthesis of Vinylferrocene

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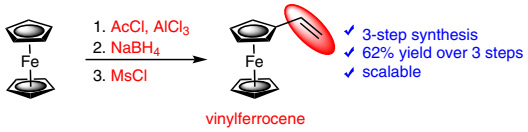

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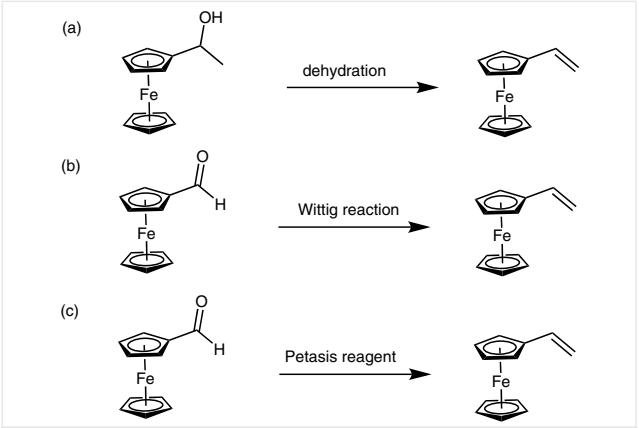
Abstract An improved, short and efficient synthesis of vinylferrocene is reported. This three-step synthesis includes Friedel–Crafts acylation, reduction, and a one-pot mesylation/elimination step to afford the target compound in 62% yield over three steps.

Key words ferrocene, Friedel–Crafts acylation, elimination, hydroamination, vinylferrocene

Ferrocene and its derivatives possess a range of useful properties, which led to their applications in catalysis, materials science, and medicine.[1–3] One of the key building blocks for incorporation of a ferrocene moiety into target structures is vinylferrocene. Vinylferrocene has been used in organic synthesis in Heck type reactions[4–9] and Diels–Alder cycloadditions.[10,11] During our research on new syntheses of chiral ferrocene derivatives, we needed access to vinylferrocene in larger quantities. Even though vinylferrocene was first reported in the 1950s, methods for its preparation are still not very convenient. Despite its deceptively simple structure, it was not easy to obtain larger quantities of vinylferrocene in good purity. Earlier publications described the synthesis of vinylferrocene by sublimation pyrolysis of the corresponding alcohol.[12–15] More recent reports such as that by Bin and co-workers described dehydration of the alcohol using copper(II) sulfate and hydroquinone in refluxing toluene to afford vinylferrocene (Scheme 1, a).[16] Other approaches to vinylferrocene involve methylenation of ferrocenecarboxaldehyde. This method, however, requires handling of a reactive Wittig reagent resulting from methyltriphenylphosphonium bromide (Scheme 1, b),[17] or even more complex formation in situ of dimethyltitanocene Cp_2TiMe_2 (Petasis reagent; Scheme 1, c).[18]

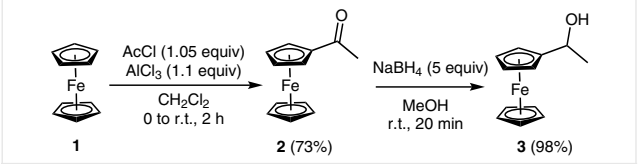
Vinylferrocene is commercially available, but its high price (typically higher than €100 per 1 g of vinylferrocene) may be prohibitive for its effective use in organic synthesis. In this context, we decided to investigate the synthesis of vinylferrocene from simple starting materials, utilizing easily available and conveniently handled reagents. In this



Scheme 1 Known procedures for the synthesis of vinylferrocene

paper, we present a multigram synthesis of vinylferrocene from ferrocene in three steps. We also show the possible utilization of vinylferrocene as a starting material for the preparation of chiral ferrocenyl amines.

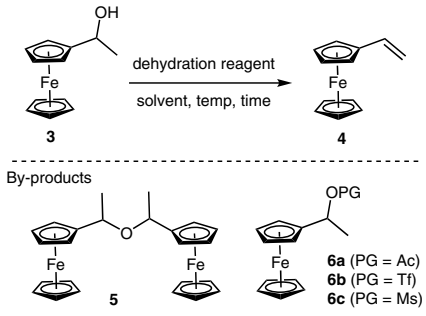
We started the synthesis of vinylferrocene by using modified reaction conditions published by Bin and co-workers.[16] First, acetylferrocene was prepared by using the well-known Friedel–Crafts acetylation protocol. Ferrocene (**1**) was treated with acetyl chloride in the presence of $AlCl_3$ as a Lewis acid, yielding the acetylferrocene (**2**) in 73% yield. Reduction of **2** with $NaBH_4$ led to the formation of hydroxyethylferrocene (**3**) in 98% yield (Scheme 2).



Scheme 2 Synthesis of hydroxyethylferrocene (**3**)

The last step of Bin's vinylferrocene synthesis was dehydration of alcohol **3** with anhydrous $CuSO_4$ in refluxing toluene. In our hands, this protocol with and without a

Dean–Stark trap gave unreliable results. We could isolate desired vinylferrocene (**4**) in up to 35% yield (Table 1, entry 1). Under these conditions, ether **5** was typically obtained as an important by-product (Scheme 3). It seems likely that dehydration depends greatly on the reaction temperature. Therefore, we have also tried other common dehydrating reagents such as anhydrous Al_2O_3 or SiO_2 (Table 1). These methods afforded only traces of vinylferrocene (**4**; Table 1, entries 2 and 3). Neither short (few minutes) nor long reaction time (48 hours) led to the successful formation of **4**.



Scheme 3 Dehydration of alcohol **3**

Table 1 Dehydration of Alcohol **3**

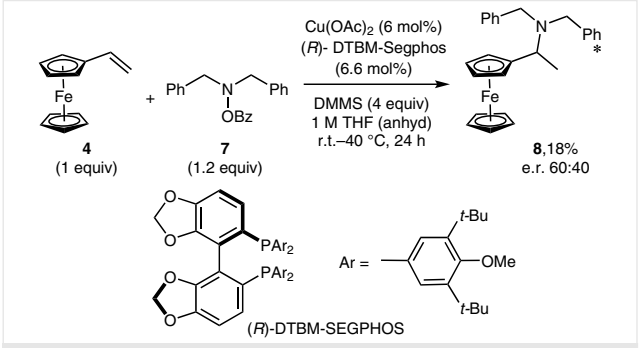
Entry	Dehydrating agent	Solvent	Temp	Time (h)	Yield of **4** (%)[a]
1	$CuSO_4$ (5 equiv)	toluene	reflux	1	35[b]
2	Al_2O_3 (10 equiv)	CH_2Cl_2	r.t.	48	trace[b]
3	SiO_2 (10 equiv)	CH_2Cl_2	r.t.	48	4 [c]
4	Ac_2O (2 equiv)	CH_2Cl_2	0 °C to r.t.	2.5	0[d]
5	Tf_2O (2.4 equiv)	CH_2Cl_2	r.t.	24	trace[b]
6	MsCl (1.05 equiv)	CH_2Cl_2	0 °C to r.t.	4	86

[a] Isolated yield.
[b] Unreacted alcohol **3** was isolated.
[c] Ether **5** (42%) and unreacted alcohol **3** (42%) were isolated.
[d] The corresponding acetic acid ester was obtained in quantitative yield.

We then focused on the transformation of the hydroxyl function to a better leaving group, such our acetate, triflate, or mesyl group (Scheme 1). Ideally, this leaving group would be labile enough to eliminate spontaneously to afford vinylferrocene. The corresponding acetate (**6a**) was formed with acetic acid anhydride in quantitative yield. However, no formation of vinylferrocene was observed when acetate **6a** was treated with bases such as NaOH or Et_3N (Table 1, entry 4). If triflic anhydride was used as protecting reagent, only traces of vinylferrocene and unreacted alcohol were isolated (entry 5). A successful result was observed after using mesyl chloride (entry 6). After 4 hours stirring of the reaction mixture at room temperature, total conversion of starting alcohol **3** was observed and, after purification, vinylferrocene (**4**) was isolated in 86% yield.

With optimum reaction conditions in hand, the large-scale synthesis was investigated. Starting from 6 grams (26.0 mmol) of alcohol **3**, we have isolated 3.85 grams (18.2 mmol, 70%) of pure vinylferrocene (**4**).

Buchwald and co-workers described a new approach to hydroamination of non-activated alkenes using copper hydride formed in situ followed by electrophilic hydroxylamine.[19] Inspired by this work, we decided to employ vinylferrocene as an alkene in the enantioselective and regioselective one-pot CuH-catalyzed hydroamination. In this reaction, vinylferrocene (**4**) was reacted with amine **7** and dimethoxymethylsilane (DMMS) under the catalysis of copper(II) acetate and a suitable ligand (Scheme 4). In an initial attempt, *rac*-BINAP (**L1**) failed to afford racemic hydroamination product *rac*-**8**. Eventually, we synthesized a racemic standard of amine **8** by nucleophilic substitution. The acetate group in **6a** was replaced with the corresponding amine (dibenzylamine) by stirring of these components at room temperature overnight in acetonitrile, yielding target racemic product *rac*-**8** in 85% yield. An enantioselective version of the hydroamination with (*R*)-DTBM-SEGPHOS ligand (**L2**) afforded only traces of the desired product, amine **8** when 2 molar equivalents of DMMS as hydride source was used. A larger amount of hydride source (4 equiv) allowed isolation of target product **8** in 18% yield and with an enantiomeric purity of 60:40 e.r. (Scheme 4). The low yield of the hydroamination product was probably due to the formation of several undesired by-products. Apart from amine **8**, we also isolated ethylferrocene (**9**) (isolated in 15% yield) and butane-2,3-diyldiferrocene (**10**) as homocoupling product of vinylferrocene (isolated in 20% yield).



Scheme 4 Application of vinylferrocene in Cu-catalyzed hydroamination

In conclusion, we have developed a laboratory-friendly synthesis of vinylferrocene in high yield (62% over three steps). This procedure also allows multigram scale synthesis and thus convenient access to larger quantities of vinylferrocene. We have also evaluated vinylferrocene as a starting material for enantioselective and regioselective one-pot

CuH-catalyzed hydroamination. Further optimization of this protocol as a new approach to chiral ferrocenyl amines is under way in our laboratory.

Anhydrous solvents were freshly distilled (CH_2Cl_2 from CaH_2, THF from Na/benzophenone). ^1H and ^{13}C NMR spectra were recorded at 600 or 300 MHz for ^1H nuclei, 150 or 75 MHz for ^{13}C nuclei. Chemical shifts are reported in δ units, parts per million (ppm); signals are referenced to TMS as internal standard. Coupling constants (*J*) are given in Hz and multiplicity is abbreviated as: s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet). HRMS were measured using heated electrospray ionization (HESI). Specific optical rotations ($[\alpha]_D^{20}$) values are reported in degrees; concentration (*c*) is in 1 g/100 mL. Reactions were monitored by thin-layer chromatography (TLC) carried out on silica or alumina plates, visualized by irradiation with UV light. Commercially available reagents were used without further purification. Synthesis of starting materials was performed according to reported procedures or is specified below.

Acetylferrocene (2)[20]

[CAS Reg. No. 1271-55-2]

To a solution of ferrocene (**1**; 5.00 g, 26.87 mmol) in anhydrous CH_2Cl_2 (30 mL), a solution of acetyl chloride (2.01 mL, 28.21 mmol) and $AlCl_3$ (3.94 g, 29.55 mmol) in anhydrous CH_2Cl_2 (40 mL) was added at 0 °C. The reaction temperature was allowed to rise to r.t., and the dark-violet solution was stirred for 2 h. The reaction was quenched by addition of ice-cold water (70 mL) at 0 °C and the mixture was extracted with CH_2Cl_2 (3 × 70 mL). The collected organic layers were washed with a solution of Na_2CO_3 (50 mL), dried over Na_2SO_4, filtrated and the solvent was removed under reduced pressure. Crude product (dark-orange solid) was purified by chromatography on SiO_2 (hexanes/EtOAc = 4:1; R_f = 0.3) to afford target product **2**.

Yield: 4.45 g (73%); orange solid; mp 85–86 °C (lit.[20] 85–86 °C).

^1H NMR (300 MHz, $CDCl_3$): δ = 4.78–4.76 (m, 2 H), 4.55–4.42 (m, 2 H), 4.20 (s, 5 H), 2.40 (s, 3 H).

NMR spectra are in agreement with those of the commercially available product.

α-Methylferrocenemethanol (3)[21]

[CAS Reg. No. 1277-49-2]

To a solution of acetylferrocene (**2**; 3.00 g, 13.15 mmol) in MeOH (75 mL), solid $NaBH_4$ (2.49 g, 65.77 mmol) was added in one portion at r.t. (CAUTION: very exothermic reaction). The reaction mixture was stirred at r.t. for 20 min. Formed solution was poured into ice-cold water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The collected organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtrated, and solvent was removed under reduced pressure to afford the crude product. Isolated alcohol **3** was characterized and used in subsequent reaction without further purification.

Yield: 2.97 g (98%); yellow-orange solid; mp 75–77 °C.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.59–4.51 (m, 1 H), 4.23–4.16 (m, 9 H), 1.83 (d, *J* = 4.8 Hz, 1 H), 1.44 (d, *J* = 6.4 Hz, 3 H).

NMR spectra are in agreement with those of the commercially available product.

Vinylferrocene (4)

[CAS Reg. No. 1271-51-8]

Under an inert atmosphere, to a solution of alcohol **3** (2.00 g, 8.69 mmol) and DMAP (53.1 mg, 0.43 mmol) in anhydrous CH_2Cl_2 (20 mL) was added dropwise Et_3N (3.64 mL, 26.1 mmol) at 0 °C, followed by addition of methanesulfonyl chloride (0.45 mL, 9.14 mmol). The reaction mixture was then stirred at r.t. for 4 h. The reaction was quenched by addition of 5% solution of $NaHCO_3$ (40 mL), and the mixture was extracted with $CHCl_3$ (3 × 100 mL). Collected organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtrated, and solvent was removed under reduced pressure to afford the crude product. The crude product was purified by chromatography on Al_2O_3 (hexanes/EtOAc, 9:1; R_f = 0.8) to afford target product **4**.

Yield: 1.59 g (86%); yellow-orange solid; mp 50–52 °C (lit.[15] 51–52 °C).

IR (ATR): 1623, 1408, 1103, 1045, 998, 894, 810, 726, 517, 477, 446 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 6.46 (dd, *J* = 17.4, 10.7 Hz, 1 H), 5.34 (d, *J* = 17.5 Hz, 1 H), 5.03 (d, *J* = 10.7 Hz, 1 H), 4.36 (s, 2 H), 4.21 (s, 2 H), 4.11 (s, 5 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 134.7, 111.1, 83.7, 69.3, 68.7, 66.8.

HRMS (ESI): *m*/*z* calcd for $[M + H^+]$ $C_{12}H_{13}Fe^+$: 213.0367; found: 213.0359.

Obtained spectral data are in agreement with those of the commercially available product.

1-(Ferrocen-3-yl)ethyl Acetate (6a)[22]

To a solution of alcohol **3** (1.00 g, 4.30 mmol) in CH_2Cl_2 (6 mL) was added dropwise Et_3N (1.21 mL, 8.70 mmol) at 0 °C, followed by slow dropping of a solution of Ac_2O (0.82 mL, 8.70 mmol) and DMAP (26.5 mg, 0.21 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was then stirred at r.t. for 2.5 h. The reaction was quenched by addition of saturated Na_2CO_3 (15 mL) and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). Collected organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtrated and solvent was removed under reduced pressure to afford the crude product. Isolated acetate **6a** was characterized and used in subsequent reaction without further purification.

Yield: 1.16 g (quant.); orange solid; mp 68–70 °C (lit.[22] 67–68 °C).

^1H NMR (600 MHz, $CDCl_3$): δ = 5.83 (q, *J* = 6.5 Hz, 1 H), 4.27–4.26 (m, 1 H), 4.22–4.22 (m, 1 H), 4.17–4.15 (m, 2 H), 4.15 (s, 5 H), 2.03 (s, 3 H), 1.56 (d, *J* = 6.5 Hz, 3 H).

***O*-Benzoyl-*N*,*N*-dibenzylhydroxylamine (7)**[23]

Product 7 was prepared according a reported procedure; mp 97–99 °C (lit[23] 96–98 °C).

***rac*-*N*,*N*-Dibenzyl-1-(ferrocenyl)ethan-1-amine (*rac*-8)**

To a solution of acetate **6a** (200 mg, 0.73 mmol) in MeCN (10 mL) was dropwise added dibenzylamine (0.28 mL, 1.46 mmol) at r.t. and the mixture was stirred overnight (20 h). The reaction was quenched by addition of H_2O (15 mL) and the mixture was extracted with $CHCl_3$ (3 × 25 mL). The collected organic layers were washed with brine (25 mL), dried over Na_2SO_4, filtrated and solvent was removed under reduced pressure to afford the crude product. Crude product was purified by chromatography on SiO_2 (hexanes/EtOAc, 10:1 + 1% Et_3N; R_f = 0.8) to afford target product *rac*-**8**.

Yield: 235 mg (85%); orange solid.

Procedure for Enantiomerically Enriched *N*,*N*-Dibenzyl-1-(ferrocenyl)ethan-1-amine [(*S*)-8]

In anhydrous THF (1 mL) was dissolved 6 mol% $Cu(OAc)_2$ (10.9 mg, 0.066 mmol) and 6.6 mol% of ligand (*R*)-DTBM-SEGPHOS (78 mg, 0.060 mmol). The mixture was stirred for 15 min at r.t., then DMMS (0.5 mL, 4 equiv, 4 mmol) was added dropwise and stirring was continued for 10 min at the same temperature. The solution of amine **7** (381 mg, 1.2 mmol) and vinylferrocene **4** (212 mg, 1 mmol) was then added by using Schlenk techniques to the tube containing the solution of [L*CuH] complex. The reaction mixture was stirred at 40 °C overnight, then the mixture was diluted with EtOAc (5 mL) and 5% solution of Na_2CO_3 (5 mL) was added dropwise. The solution was extracted with EtOAc (3 × 25 mL), the collected organic layers were washed with brine (25 mL), dried over Na_2SO_4, filtrated, and the solvent was removed under reduced pressure to afford the crude product. The crude product was purified by chromatography on SiO_2 (hexanes/EtOAc, 30:1 + 1% Et_3N; R_f = 0.4) to afford target product **8**.

Yield: 68 mg (18%); orange solid; mp 62–65 °C; $[\alpha]_D^{20}$ –14.5 (*c* 1.00, $CHCl_3$); HPLC analysis (Chiralcel OD-H; hexane/^{i}PrOH, 99:1; 0.8 mL/min; 254 nm) indicated 20% ee: t_R = 5.9 (major), 6.5 (minor) min.

IR (ATR): 1234, 1103, 1068, 1022, 998, 822, 749, 728, 697, 514, 487 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 7.4 Hz, 4 H, -Ph), 7.31 (t, *J* = 7.6 Hz, 4 H, -Ph), 7.23 (t, *J* = 7.3 Hz, 2 H, -Ph), 4.27–4.27 (m, 1 H, Fc), 4.18–4.14 (m, 3 H, Fc), 4.02 (s, 5 H, Cp^{Fc}), 3.81 (q, *J* = 6.9 Hz, 1 H, H_α), 3.53 (d, *J* = 14.1 Hz, 2 H, CH_2-Ph), 3.36 (d, *J* = 14.1 Hz, 2 H, -CH_2-Ph), 1.47 (d, *J* = 6.9 Hz, 3 H, -CH_3).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 140.9 (2×C, Cq^{Ph}), 128.6 (4×C, -Ph), 128.2 (4×C, -Ph), 126.7 (2×C, -Ph), 88.9 (Cq^{Fc}), 69.1 (-CH^{Fc}), 68.7 (5×C, Cp^{Fc}), 67.6 (-CH^{Fc}), 67.1 (-CH^{Fc}), 66.9 (-CH^{Fc}), 52.3 (2×C, -CH_2-Ph), 52.2 (-CH_α), 15.4 (-CH_3).

HRMS (ESI): *m*/*z* calcd for $[M + H^+]$ $C_{26}H_{28}FeN^+$: 410.1571; found: 410.1565.

Butane-2,3-diyldiferrocene (10)

^1H NMR (600 MHz, $CDCl_3$): δ = 4.09 (s, 5 H, Cp^{Fc}), 4.07 (br s, 2 H, Fc), 4.05 (s, 5 H, Cp^{Fc}), 3.99 (br s, 2 H, Fc), 3.94 (br s, 1 H, Fc), 3.85 (br s, 1 H, Fc), 3.74 (br s, 1 H, Fc), 2.63–2.59 (m, 2 H, H_α), 1.15 (d, *J* = 6.6 Hz, 3 H, -CH_3), 1.05 (d, *J* = 6.6 Hz, 3 H, -CH_3).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 93.8 (Cq^{Fc}), 92.6 (Cq^{Fc}), 68.8 (-CH^{Fc}), 68.8 (5×C, Cp^{Fc}), 68.4 (5×C, Cp^{Fc}), 68.1 (-CH^{Fc}), 67.0 (-CH^{Fc}), 66.9 (-CH^{Fc}), 66.8 (-CH^{Fc}), 66.7 (-CH^{Fc}), 66.6 (-CH^{Fc}), 66.4 (-CH^{Fc}), 40.9 (-CH_α), 40.8 (-CH_α), 16.3 (-CH_3), 14.3 (-CH_3).

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Supporting Information

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