Stereoselective synthesis of chiral, non-racemic 1,2,3-tri- and 1,3-disubstituted ferrocene derivatives

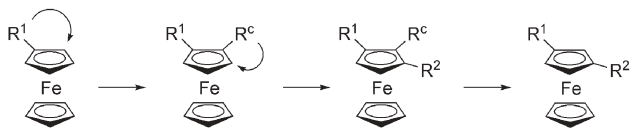
Marianne Steurer, Karin Tiedl, Yaping Wang and Walter Weissensteiner*

Received (in Cambridge, UK) 22nd June 2005, Accepted 9th August 2005
First published as an Advance Article on the web 7th September 2005
DOI: 10.1039/b508761a

Chiral, non-racemic 1,2,3-trisubstituted ferrocene derivatives are accessible from monosubstituted ferrocenes through two sequential *ortho*-deprotonation reactions; removal of the central substituent gives 1,3-disubstituted ferrocenes.

Chiral non-racemic ferrocene derivatives have found broad application as ligands for homogeneous enantioselective catalysts.[1] In this respect, 1,2-disubstituted ferrocenes are mainly used but 1,1′,2-tri- or 1,1′,2,2′-tetrasubstituted ferrocenes are also employed. In general, ferrocenes with such substitution patterns are usually prepared from mono- or 1,1′-disubstituted precursors by stereoselective *ortho*-metallation reactions.[2] Interestingly, applications of chiral non-racemic 1,3-disubstituted ferrocenes are very rare and this might be due to the fact that suitable methods for the synthesis of such derivatives are lacking.[3] Only recently, in the context of ferrocene-based pincer ligands,[4] Brown and co-workers reported a broadly applicable method for the synthesis of achiral or racemic 1,3-disubstituted ferrocene derivatives, with the key step of this reaction sequence being a selective *meta*-lithiation of ferrocenyl-tolyl sulfide.[5] Attempts to carry out this reaction in an enantioselective manner have not yet been successful and, in addition, methods for separating the enantiomers of racemic mixtures are very limited.[5,6] For these reasons we became interested in the development of general and preparatively useful methods for the synthesis of chiral, non-racemic 1,3-disubstituted ferrocenes.

In our search for suitable methods, we investigated the reaction sequence depicted in Scheme 1: starting from a suitable monosubstituted ferrocene derivative (Fc-R^1), 1,2,3-trisubstituted intermediates are built up in two steps, both of which involve *ortho*-deprotonation reactions. Subsequent removal of the central substituent (R^c) gives 1,3-disubstituted ferrocenes. R^1 can be chosen from a broad selection of *ortho*-directing groups[1,2] but the central substituent R^c must be both *ortho*-directing *and* removable. Possible candidates for R^c are the halides (chloride[7] and bromide[8]) as well as sulfinyl and sulfonyl groups.[9] In our opinion bromide was best suited for this purpose and it was therefore tested in three reaction sequences in combination with substituents (R^1) 1-dimethylaminoethyl [CH(NMe$_2$)Me], the ephedrine derivative CH$_2$N(Me)CH(Me)CH(Ph)OMe and the *p*-tolylsulfinyl [4-CH$_3$C$_6$H$_4$S(O)] unit.

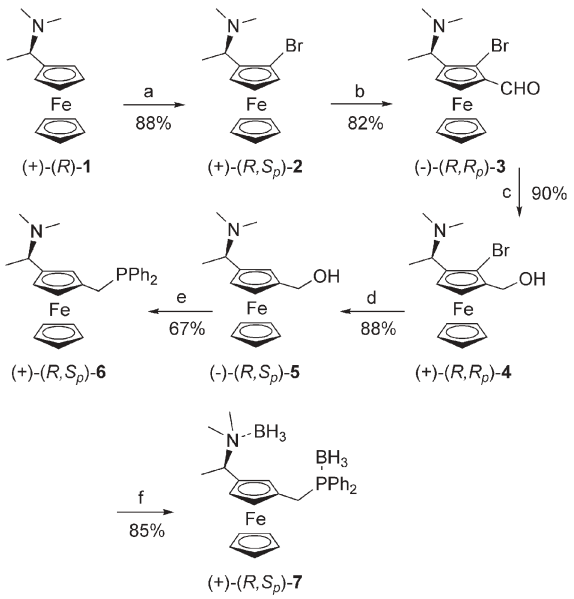


Scheme 1 General reaction scheme for the synthesis of 1,2,3-tri- and 1,3-disubstituted ferrocenes.

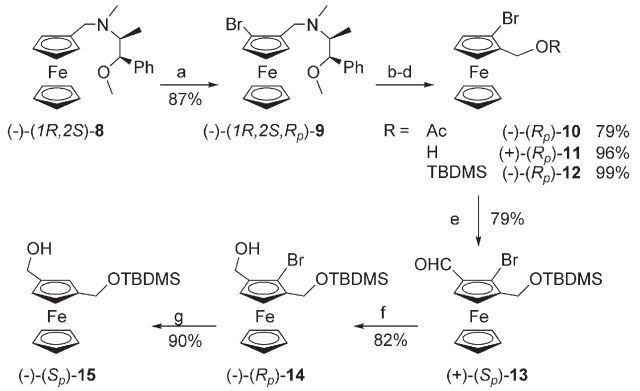
Universität Wien, Fakultät für Chemie, Währinger Straße 38, Wien, A-1090, Austria. E-mail: walter.weissensteiner@univie.ac.at

In the first reaction sequence [R^1 = CH(NMe$_2$)Me and R^c = Br (Scheme 2)] commercially available (*R*)-*N*,*N*-(1-dimethylaminoethyl)ferrocene [Ugi's amine, (*R*)-**1**] was reacted using a literature procedure[10] with *s*-BuLi and F$_2$BrCCBrF$_2$ to give (*R*,*S*$_p$)-**2** in 88% yield. In order to optimise the subsequent deprotonation step with respect to temperature and the amount of base, different conditions were applied to the reaction of (*R*,*S*$_p$)-**2** with Li-TMP (TMP = 2,2,6,6-tetramethyl piperidine) as the base and ClSiMe$_3$ as the electrophile.

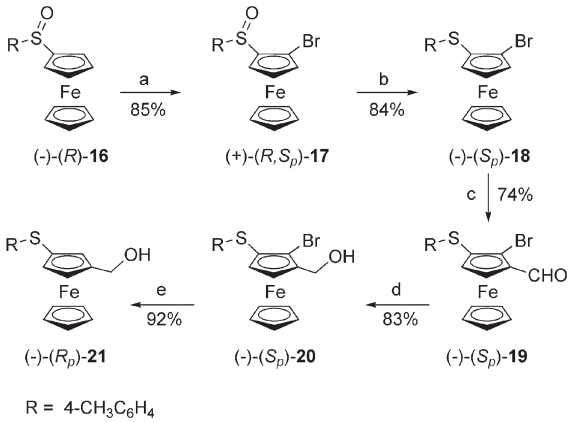
The use of these optimised conditions†and dimethylformamide as the electrophile gave aldehyde (*R*,*R*$_p$)-**3** exclusively (82%). Reduction of this compound with LiAlH$_4$ gave alcohol (*R*,*R*$_p$)-**4** in 90% yield and subsequent reaction with 2.5 equivalents of *n*-BuLi and H$_2$O resulted in the 1,3-disubstituted ferrocenyl aminoalcohol (*R*,*S*$_p$)-**5** (88%). It is clear that a variety of analogous derivatives of



Scheme 2 Synthesis of 1,3-disubstituted ferrocenes; reaction sequence 1. (a) *s*-BuLi, Et$_2$O, 0 °C, 4 h; −78 °C, F$_2$BrCCBrF$_2$, THF, rt, 17 h, 88%; (b) Li-TMP, THF, −78 °C 30 min, −30 °C 3 h; DMF, 0 °C 16 h, 82%; (c) 0 °C, LiAlH$_4$, THF, rt, 16 h, 90%; (d) −78 °C, *n*-BuLi, 0 °C 30 min, H$_2$O, 88%; (e) HPPh$_2$, CH$_2$Cl$_2$, HBF$_4$, rt 16 h, 67%; (f) BH$_3$·THF, rt 16 h, 85%. TMP = 2,2,6,6-tetramethylpiperidine, DMF = *N*,*N*-dimethylformamide. Overall yield **1** → **5**: 57%.



Scheme 3 Synthesis of 1,3-disubstituted ferrocenes; reaction sequence 2. (a) *t*-BuLi, pentane, −78 °C 1.5 h, −30 °C 2.5 h; $F_2BrCCBrF_2$, THF, −78 °C 30 min, rt 16 h, 87%; (b) Ac_2O, 150 °C 3 h, 79%; (c) K_2CO_3, MeOH, 45 °C 3.5 h, 96%; (d) 0 °C, *t*-Bu(Me)$_2$SiCl, imidazole, DMF, rt 17 h, 99%; (e) Li-TMP, THF, −78 °C 30 min, −30 °C 3 h; DMF, 0 °C 1 h, 79%; (f) 0 °C, $LiAlH_4$, THF, rt 16 h, 82%; (g) −78 °C, *n*-BuLi, 0 °C 30 min, H_2O, 90%. TBDMS = *t*-butyldimethylsilyl. Overall yield **8** → **15**: 38 %.



Scheme 4 Synthesis of 1,3-disubstituted ferrocenes; reaction sequence 3. (a) LDA, THF, −78 °C 3 h; $F_2BrCCBrF_2$, THF, −78 °C 30 min, rt 19 h, 85%; (b) NaI (6 equiv), Me_3SiCl (12 equiv), CH_3CN, rt 18 h, 84%; (c) Li-TMP, THF, −78 °C 30 min, −30 °C 3 h; DMF, 0 °C 1 h, 74%; (d) $LiAlH_4$, THF, 0 °C 1.5 h, 83%; (e) −78 °C, *n*-BuLi, 0 °C 30 min, H_2O, 92%. Overall yield **16** → **21**: 40%.

3, **4** and **5** can be accessed by either using different electrophiles in the *ortho*-deprotonation step of **2** or by functional group tranformation of **4** and **5** or their analogues. As an example, we synthesised a potential pincer ligand,[4] the aminophosphine (R,S_p)-**6** (67%),[11] as well as its bisborane complex (R,S_p)-**7** (85%).

The second reaction sequence [R^1 = $CH_2N(Me)CH(Me)$-CH(Ph)OMe and R^c = Br (Scheme 3)] starts from an *O*-methylephedrine-substituted ferrocene derivative and allows the synthesis of exclusively planar chiral, non-racemic 1,3-disubstituted ferrocenes. Monosubstituted ferrocene derivative (1*R*,2*S*)-**8**, which is easily accessible from *N*-ferrocenylmethyl-*N,N,N*-trimethylammonium iodide and *O*-methylephedrine,[12] was reacted with *t*-BuLi and $F_2BrCCBrF_2$ to give (1*R*,2*S*,R_p)-**9** in 87% yield and 98% d.e. All attempts to selectively *ortho*-deprotonate bromide **9** led to product mixtures and, in an effort to overcome this problem, the *O*-methylephedrine unit was replaced by a *tert*-butyldimethylsilyl-protected hydroxyl group (Scheme 3, **9** → **12**, 75%).[13] In this case, the use of the reaction conditions optimised for **2** enabled the selective transformation of bromide (R_p)-**12** into aldehyde (S_p)-**13** (79%) which, after reduction with $LiAlH_4$, gave alcohol (R_p)-**14** (82%). Finally, reaction with *n*-BuLi and H_2O removed the bromide and gave the 1,3-disubstituted ferrocene derivative (S_p)-**15** in 90% yield. In this case it is also expected that derivatives **14** and **15** (like **4** and **5**) can serve as enantiopure starting materials for a number of related products—including pincer ligands.

In the third reaction sequence the use of bromide as the central substituent was combined with the *ortho*-directing *p*-tolylsulfinyl substituent [R^1 = 4-$CH_3C_6H_4S(O)$ and R^c = Br (Scheme 4)]. Bromide (R,S_p)-**17** was prepared by reacting *p*-tolyl-ferrocenyl sulfoxide[14] (*R*)-**16** with LDA and $F_2BrCCBrF_2$ (85%)[15] and the product was subsequently reduced with sodium iodide and chlorotrimethylsilane to give sulfide (S_p)-**18** (84%). As in the cases of **2** and **12**, ferrocene derivative **18** could be selectively deprotonated adjacent to the bromide substituent and subsequent reaction with DMF gave aldehyde (S_p)-**19** in 74% yield. Reduction with $LiAlH_4$ resulted in alcohol (S_p)-**20**, which on reaction with *n*-BuLi led to the desired 1,3-disubstituted ferrocene derivative (R_p)-**21** (92%). As recently reported for its racemate,[5] **21** can easily be functionalised and can therefore serve as a valuable starting material for a variety of chiral, non-racemic 1,3-disubstituted ferrocene derivatives. This approach should also be applicable to compound **20** or analogues that are accessible from **18** with different electrophiles.

In summary we have demonstrated that chiral non-racemic 1-R^1,2-R^c,3-R^2-trisubstituted ferrocenes can be synthesised in two steps from monosubstituted ferrocenes Fc-R^1 with both steps involving *ortho*-deprotonations. Particularly combinations of stereoselectively *ortho*-directing groups R^1 with bromide as the central substituent gave products with very high selectivity and in preparatively useful yields. Since bromide can easily be removed from 1-R^1,2-Br,3-R^2-trisubstituted ferrocenes, chiral non-racemic 1-R^1,3-R^2-disubstituted ferrocenes become accessible *via* this route. We assume that our method can be further extended with respect to both the *ortho*-directing groups R^1 and the electrophiles used in order to introduce substituent R^2. Furthermore, functional group variations of R^1 and R^2 as well as of bromide will make easily available a variety of 1,2,3-tri- and 1,3-disubstituted ferrocenes for new applications.

The authors thank Solvias AG for a donation of Ugi's amine and the undergraduate students Martin Fritzenwanker, Christian Kowol, Katrin Prantz, Michael Reithofer and Raffael Schuecker for their enthusiastic help in synthesising a variety of ferrocene derivatives.

Notes and references

† Typical procedure for the *ortho*-deprotonation of (R,S_p)-**2**: The reaction was carried out under an argon atmosphere using standard vacuum line and Schlenk techniques. To a cooled (−78 °C) degassed solution of (R,S_p)-**2** (500 mg, 1.488 mmol) in THF (5 mL) was added dropwise a solution of Li-TMP in THF (0.7 M, 4.25 mL, 2.976 mmol). The reaction mixture was stirred for 30 min at −78 °C followed by 3 h at −30 °C. The reaction temperature was lowered to −78 °C and dimethylformamide (350 μL, 4.516 mmol) was added. The temperature was raised to 0 °C and stirring continued for 16 h at this temperature. The reaction was quenched with saturated aqueous Na_2CO_3 (15 mL) and diethyl ether was added. The phases were separated and the aqueous phase was extracted 3 times with

diethyl ether. The combined organic phases were washed with brine, dried ($MgSO_4$) and the solvents removed under reduced pressure. The residue was purified by column chromatography on alumina. A mixture of petroleum ether (boiling range 69–72 °C), ethyl acetate and triethylamine (30 : 10 : 1) was used as the eluent to give product (R,R_p)-**3** as a red oil (442 mg, 82%) . Selected characterisation data. (R,R_p)-**3**: δ_H(400.1 MHz; $CDCl_3$; $CHCl_3$; ppm) 1.47 (3 H, d, *J* 6.9, $CHCH_3$), 2.17 (6 H, s, $N(CH_3)_2$), 3.87 (1 H, q, *J* 6.9, $CHCH_3$), 4.25 (5 H, s, Cp′), 4.61 (1 H, d, *J* 2.8, Cp-H4), 4.90 (1 H, d, *J* 2.8, Cp-H3), 10.22 (1 H, s, CHO); δ_C(100.6 MHz; $CDCl_3$; $CDCl_3$; ppm) 15.81 (CH_3), 41.04 ($N(CH_3)_2$), 55.65 (CH), 65.63 (Cp-C3), 69.59 (Cp-C4), 72.84 (Cp′), 75.29, 92.94 (2 Cp-C_q), 193.94 (CHO), 1 Cp-C_q not observed; *m*/*z* (EI, 60 °C) 362.9928 (M^+, 30%; $C_{15}H_{18}BrFeNO$ requires 362.9923), 321/319 (6), 268 (28), 239 (54), 212 (16); $[\alpha]_\lambda^{20}$ −720 (589 nm), −806 (578), −1334 (546) (*c* 0.128 in $CHCl_3$). (R,S_p)-**5**: yellow powder; mp 121−123 °C; δ_H(400.1 MHz; $CDCl_3$; $CHCl_3$; ppm) 1.42 (3 H, d, *J* 6.9, $CHCH_3$), 1.71 (1 H, br s, OH), 2.09 (6 H, s, $N(CH_3)_2$), 3.57 (1 H, q, *J* 6.9, $CHCH_3$), 4.12 (1 H, m, Cp-H4), 4.12 (5 H, s, Cp′), 4.21 (1 H, m, Cp-H5), 4.25 (1 H, t, *J* 1.4, Cp-H2), 4.33 (2 H, s, CH_2OH); δ_C(100.6 MHz; $CDCl_3$; $CDCl_3$; ppm) 15.55 ($CHCH_3$), 40.62 ($N(CH_3)_2$), 58.54 ($CHCH_3$), 60.88 (CH_2OH), 66.96, 66.99 (Cp-C4, Cp-C5), 69.00 (Cp′), 69.12 (Cp-C2), 87.75, 87.89 (2 Cp-C_q); *m*/*z* (EI, 70 °C) 287.0980 (M^+, 81%; $C_{15}H_{21}FeNO$ requires 287.0973), 272 (25), 243 (90), 225 (27), 134 (100). $[\alpha]_\lambda^{20}$ −1.2 (589 nm), −1.6 (578), −7.9 (546) (*c* 0.674 in $CHCl_3$). (S_p)-**15**: yellow powder; mp 55–59 °C; δ_H(400.1 MHz; $CDCl_3$; $CHCl_3$; ppm) 0.08 [6 H, s, 2 $Si(CH_3)_2C(CH_3)_3$], 0.93 [9 H, s, $Si(CH_3)_2C(CH_3)_3$], 1.49 (1 H, t, *J* 5.9, OH), 4.15 (5 H, s, Cp′), 4.19 (1 H, dd, *J* 2.0 and 1.3, Cp-H4), 4.22 (1 H, dd, *J* 2.0 and 1.3, Cp-H5), 4.29 (2 H, d, *J* 5.9, CH_2OH), 4.30 (1 H, t, *J* 1.3, Cp-H2), 4.41 (2 H, s, $CH_2OTBDMS$); δ_C(100.6 MHz; $CDCl_3$; $CDCl_3$; ppm) −5.16 (2C $Si(CH_3)_2C(CH_3)_3$], 18.37 [C_q, $Si(CH_3)_2C(CH_3)_3$], 25.97 [3 C $Si(CH_3)_2C(CH_3)_3$], 60.75 (CH_2OH), 61.16 ($CH_2OTBDMS$), 67.52 (Cp-C4), 67.73 (Cp-C2), 68.03 (Cp-C5), 68.82 (Cp′), 88.43, 88.46 (2 Cp-C_q); *m*/*z* (EI, 80 °C) 360.1197 (M^+, 100%; $C_{18}H_{28}FeO_2Si$ requires 360.1208), 285 (3), 229 (19), 195 (20), 91 (49), 75 (28). $[\alpha]_\lambda^{20}$ −6.9 (589 nm), −6.5 (578), −9.1 (546) (*c* 0.583 in $CHCl_3$). (R_p)-**21**: yellow powder; mp 62–68 °C; δ_H(400.1 MHz; $CDCl_3$; $CHCl_3$; ppm) 1.57 (1 H, t, *J* 5.8, OH), 2.27 (3 H, s, $CH_3C_6H_4$), 4.27 (5 H, s, Cp′), 4.34 (2 H, d, *J* 5.8, CH_2OH), 4.39 (1 H, dd, *J* 2.4 and 1.5, Cp-H4), 4.41 (1 H, dd, *J* 2.4 and 1.5, Cp-H5), 4.48 (1 H, t, *J* 1.5, Cp-H2), 6.98–7.02 (2 H, m, C_6H_4-H_{ortho}), 7.02–7.06 (2 H, m, C_6H_4-H_{meta}); δ_C(100.6 MHz; $CDCl_3$; $CDCl_3$; ppm) 20.88 ($CH_3C_6H_4$), 60.51 (CH_2), 69.44 (Cp-C4), 69.99 (Cp′), 74.26 (Cp-C2), 74.83 (Cp-C5), 77.36, 90.05 (2 C, Cp-C_q), 126.94 (2 C,C_6H_4-C_{meta}), 129.43 (2 C, C_6H_4-C_{ortho}), 135.19, 136.36 (2 C, C_6H_4-C_q); *m*/*z* (EI, 100 °C) 338.0424 (M^+, 100%; $C_{18}H_{18}FeOS$ requires 338.0428), 200 (85), 185 (37), 167 (15), 138 (11), 121 (19); $[\alpha]_\lambda^{20}$ −43.3 (589 nm), −44.1 (578), −43.7 (546) (*c* 0.513 in $CHCl_3$).

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