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Synthesis of new ferrocene derivatives with rod-like structure

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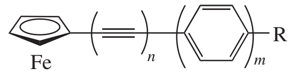
The Suzuki–Miyaura cross-coupling of tris(4-ferrocenylphenyl)- and tris[4-(2-ferrocenylethynyl)phenyl]boroxines with functionalized iodoarenes gives new ferrocene derivatives of rod-like structure.

Previously,[1] we reported on the preparation of a series of rod-like compounds containing a biphenyl or terphenyl moiety bound to ferrocenyl, which revealed liquid crystalline properties. Bulky and easily polarizable ferrocene substituent often drastically changes the mesomorphic behavior of liquid crystals. The advantage of ferrocene is the stability of its oxidized and reduced forms and a low red-ox potential. Thus, ferrocene is an ideal redox sensor and permits to develop a homogeneous competitive assay. Among known tracers,[2–4] the ferrocenyl group is drawn close to the site of contact between tracer and antibody and this proximity can affect the red-ox transitions of ferrocenyl group up to the complete deactivation.[3] Consequently, it is important to design new markers, with a ferrocenyl group being withdrawn from the 'anchor'.

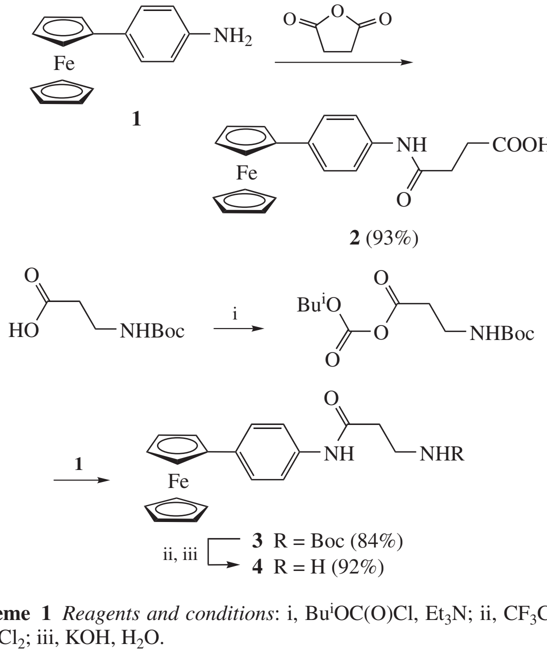


A

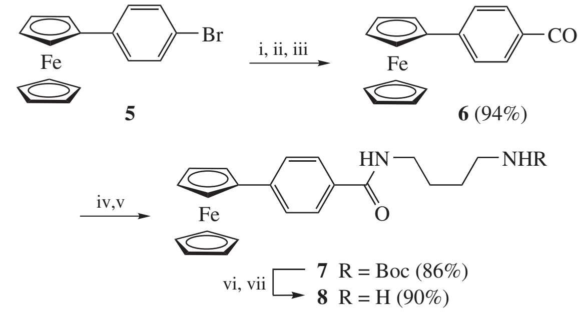
n = 0, 1; m = 1–3

R = OH, NH_2, $(CH_2)_3COOH$, $NHC(O)CH_2CH_2COOH$,
$C(O)NH(CH_2)_4NH_2$, $NHC(O)CH_2CH_2NH_2$

Here we report on the syntheses of new ferrocene derivatives **A** which possess a rod-like structure and contain 'anchoring' amino or carboxyl groups. The target compounds with one benzene ring bound directly to ferrocenyl and flexible spacer were prepared as shown in Schemes 1 and 2, starting from the accessible 4-ferrocenylaniline **1** and 4-bromophenylferrocene **5**. In these cases, usual methods of peptide synthesis were used providing excellent yields.

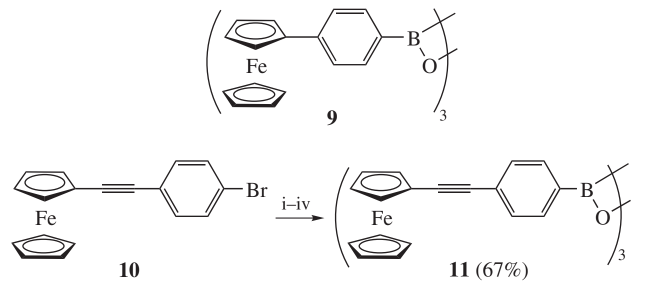


Scheme 1 *Reagents and conditions*: i, $Bu^iOC(O)Cl$, Et_3N; ii, CF_3COOH, CH_2Cl_2; iii, KOH, H_2O.



Scheme 2 *Reagents and conditions*: i, BuLi, THF, –60 °C; ii, CO_2; iii, HCl, H_2O; iv, $(COCl)_2$; v, $BocNH(CH_2)_4NH_2$, Et_3N, –18 °C; vi, CF_3COOH, CH_2Cl_2; vii, KOH, H_2O.

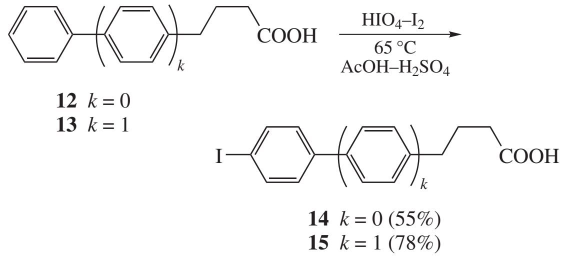
Elongation of the rod-like fragment in the target compounds was achieved by introduction of additional phenylene and acetylene moieties on using the Suzuki–Miyaura cross-coupling. One of the reactants, tris(4-ferrocenylphenyl)boroxine **9** (Scheme 3), was prepared previously.[5] Introduction of a triple carbon–carbon bond in the molecule was achieved by the use of a new boroxine **11** (Scheme 3) which was synthesized[†] from bromo derivative **10** available by direct alkynylation of ferrocene.[6]



Scheme 3 *Reagents and conditions*: i, BuLi, –60 °C; ii, $(BuO)_3B$, –60 °C; iii, HCl, H_2O; iv, azeotropic dehydration with xylene.

[†] *Tris[4-(ferrocenylethynyl)phenyl]boroxine* **11**. A solution of 2.01 M *n*-butyllithium (2 ml, 4.02 mmol) was added to a solution of 1-(4-bromophenyl)-2-ferrocenylacetylene **10** (1.27 g, 3.48 mmol) at –60 °C in argon purge. The deep brick colored reaction mixture was stirred at –55 to –60 °C for 1 h resulting in an orange suspension of 4-ferrocenylethynylphenyllithium. Tri-*n*-butyl borate (1.31 ml, 4.77 mmol) was added at

Iodoarenes **14** and **15** were synthesized by iodination of the corresponding arenes **12** and **13** according to a modified published procedure[7,8] (Scheme 4).

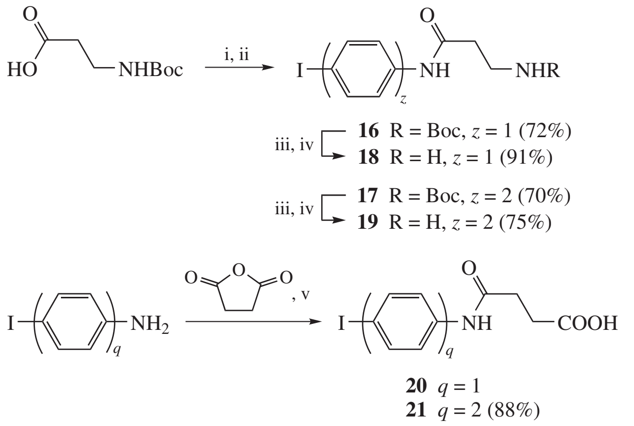


12 $k = 0$
13 $k = 1$

14 $k = 0$ (55%)
15 $k = 1$ (78%)

Scheme 4

Common methods of organic synthesis were used in preparation of iodo precursors **18–21** (Scheme 5).



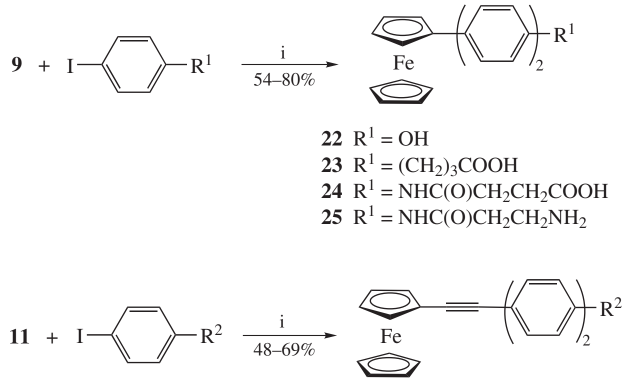
16 R = Boc, $z = 1$ (72%)
18 R = H, $z = 1$ (91%)
17 R = Boc, $z = 2$ (70%)
19 R = H, $z = 2$ (75%)

20 $q = 1$
21 $q = 2$ (88%)

Scheme 5 *Reagents and conditions*: i, $Bu^iOC(O)Cl$, Et_3N, –18 °C; ii, $I(C_6H_4)_zNH_2$ ($z = 1, 2$), –18 °C; iii, CF_3COOH, CH_2Cl_2; iv, KOH; v, CH_2Cl_2, reflux.

Starting from boroxines **9**, **11** and different iodoarenes, markers containing biphenyl moiety were synthesized by palladium-catalyzed cross-coupling (Scheme 6).[‡] Note that attempted preparation of similar terphenyl derivatives from boroxines **9** and **11** and iodobiphenyls **15**, **19**, **21** was unsuccessful.[§]

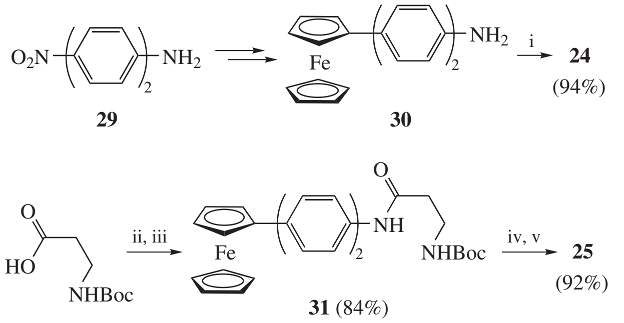
Thus obtained 4′-ferrocenyl[1,1′]biphenyl-4-amine **30** was converted into compounds **24** and **25** (Scheme 7).



22 $R^1 = OH$
23 $R^1 = (CH_2)_3COOH$
24 $R^1 = NHC(O)CH_2CH_2COOH$
25 $R^1 = NHC(O)CH_2CH_2NH_2$

26 $R^2 = NO_2$
27 $R^2 = NH_2$
28 $R^2 = (CH_2)_3COOH$

Scheme 6 *Reagents and conditions*: i, 5 mol% $Pd(PPh_3)_4$, K_2CO_3, DMF, H_2O, 60 °C.



29
30
31 (84%)

Scheme 7 *Reagents and conditions*: i, succinic anhydride, CH_2Cl_2; ii, $Bu^iOC(O)Cl$, Et_3N, –18 °C; iii, **30**; iv, CF_3COOH, CH_2Cl_2; v, KOH.

To conclude, detailed procedures were developed for the preparation of a range of ferrocenyl compounds with a rod-like structure. The compounds obtained can find applications as precursors for new calamitic liquid crystals, and the anchor groups permit their further modification, such as elongation of molecule, and as electrochemical markers, for example, in immunoanalysis.

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Online Supplementary Materials

Supplementary data associated with this article (synthetic procedures and characteristics of compounds **2–4**, **6–8**, **12**,

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–60 °C to the suspension within 2 min. The precipitate of lithium derivative dissolved and the reaction mixture became brown. The mixture was allowed to warm gradually to –10 °C in 1 h, then to ambient temperature and stirring was continued for 1 h. Water (2 ml) was added followed by a solution of hydrochloric acid (0.7 ml) in water (8.5 ml). Organic layer was separated, diluted with benzene, washed with water, dried over sodium sulfate and evaporated under reduced pressure. Mixture of xylenes (25 ml) was added to the residue and the solvent was evaporated again under reduced pressure at bath temperature 93 °C. Dry residue was washed with hot light petroleum and dried in air to give boroxine **11** (0.74 g, 68%) as an orange powder, decomp. over 205 °C. ^{1}H NMR ($CDCl_3$) δ: 4.24 and 4.27 (m and s, 2H + 5H, C_5H_4, C_5H_5), 4.55 (m, 2H, C_5H_4), 7.60–7.62 and 8.17–8.19 (m, 4H, AA′BB′, C_6H_4). ^{13}C NMR ($CDCl_3$) δ: 64.88 (C_{ipso}, C_5H_4), 69.07 (CH, C_5H_4), 70.05 (CH, C_5H_5), 71.57 (CH, C_5H_4), 85.95, 94.50 (C≡C), 128.30 (C_{ipso}, C_6H_4), 130.80 (C_{ipso}, C_6H_4), 133.36 (CH, C_6H_4), 135.45 (CH, C_6H_4). MS (MALDI-TOF), *m/z*: 936.120 [M$^+$] (calc., *m/z*: 936.1226). Found (%): C, 69.19; H, 4.29. Calc. for $C_{54}H_{39}Fe_3B_3O_3$ (%): C, 69.30; H, 4.20.

[‡] *4-(4′-Ferrocenylethynyl[1,1′]biphenyl-4-yl)butanoic acid* **28**. A mixture of boroxine **11** (0.168 g, 0.18 mmol), iodoarene **14** (0.157 g, 0.54 mmol), potassium carbonate (0.193 g, 1.35 mmol), $Pd(PPh_3)_4$ (0.017 g, 0.015 mmol), DMF (10 ml) and 1 ml of water was stirred at 60 °C for 12 h in argon purge. After cooling to ambient temperature, the mixture was poured into a mixture of dichloromethane (25 ml) and water (25 ml) and acidified to pH 3 with conc. HCl. Organic layer was separated, water layer was extracted with dichloromethane (3×20 ml). Combined organic extracts were thoroughly washed with water to remove DMF, dried over Na_2SO_4 and evaporated to dryness. The residue was subjected to column chromatography on silica gel. Using benzene two yellow bands were eluted and discarded. Subsequent elution with benzene–ethyl acetate (1 : 1) afforded acid **28** (0.115 g, 47%), mp 211–212 °C. ^{1}H NMR (DMSO-d_6) δ: 4.25 (m, 2H + 5H, C_5H_4, C_5H_5), 4.51 (m, 2H, C_5H_4), 7.25 (m, 4H, C_6H_4), 7.53 (m, 4H, C_6H_4). ^{13}C NMR (DMSO-d_6) δ: 29.70 ($CH_2CH_2CH_2$), 34.63 (CH_2COOH), 34.63 ($CH_2C_6H_4$), 85.66 and 88.98 (C≡C), 66.84 (2C, C_5H_4), 69.99 (C_5H_5), 71.42 (2C, C_5H_4), 125.29, 125.71, 126.76, 126.97, 129.00, 131.77, 138.28, 140.62 (Ar). MS (MALDI-TOF), *m/z*: 448.114 [M$^+$] (calc., *m/z*: 448.1126). Found (%): C, 75.16; H, 5.78. Calc. for $C_{28}H_{24}O_2Fe$ (%): C, 75.01; H, 5.39.

[§] Although the reactants were consumed during cross-coupling, purification of the terphenyl products was impossible due to their very low solubility. However, MALDI data confirmed formation of cross-coupling products.

14–19, **21–27**, **29** and **31**) can be found in the online version at doi:10.1016/j.mencom.2015.03.010.

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