Selective functionalization of the 1′-position in ferrocenecarbaldehyde

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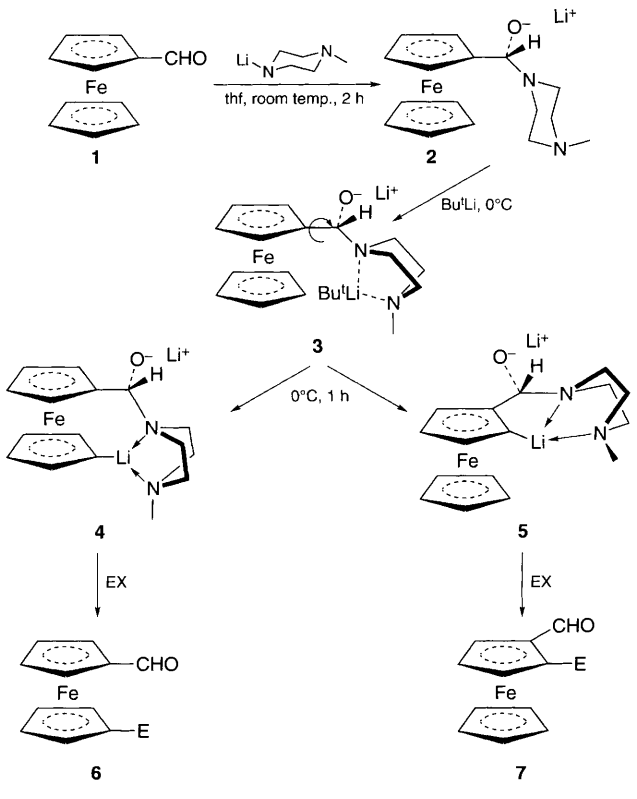
An efficient and selective new method for the preparation of unsymmetrical 1,1′-disubstituted ferrocenes by a one-pot procedure, starting from ferrocenecarbaldehyde, is disclosed.

In recent years, the chemistry of ferrocene and the design of new compounds containing the ferrocene unit has received a surge in interest, owing to their utility in many fields such as organic synthesis, catalysis and materials chemistry.[1,2] Among the interesting compounds being made are those in which the two cyclopentadienyl rings of the ferrocene bear different substituents. Recently Wright[3] and Lai and Dong[4] described novel methods for the synthesis of unsymmetrical 1,1′-disubstituted ferrocenes. Both methods involve selective transformation of one substituent of symmetrical 1,1′-disubstituted compounds. Wright reported the selective transmetallation of one tri-*n*-butylstannyl group of [Fe(η^5-$C_5H_4SnBu_3)_2$] and Lai and Dong described the selective monolithiation of 1,1′-dibromoferrocene. We report here a novel practical method for preparing unsymmetrical 1,1′-disubstituted ferrocenes by selective introduction of a second substituent in the 1′ position of ferrocenecarbaldehyde.

In keeping with our studies[5] concerning the design of ferrocene-containing compounds with non-linear optical (NLO) properties, we were looking for a practical and selective method for introduction of a second substituent on the 2 position of ferrocenecarbaldehyde. Usually orthometallation reactions require the presence of a directing group like amine,[6] oxazoline,[7] sulfoxide[8] or acetal.[9,10] In 1981 Comins and Brown[11] described an efficient and straightforward method for the ortholithiation of benzaldehydes using an aminal moiety as a temporary 'protecting–directing group'. We decided to look at the possibility of applying of this method to the ortholithiation of ferrocenecarbaldehyde. Instead of the expected reaction in the *ortho*-position, we serendipitously discovered a new method for functionalizing the 1′ position of ferrocenecarbaldehyde with good yields and very high selectivity (Scheme 1).



Scheme 1

Treatment of **1** with 1 equiv. of the lithium salt of *N*-methylpiperazine in thf solution produced the aminal anion **2**. Subsequent treatment of **2** with Bu^{t}Li (1 equiv.) followed by reaction with various electrophiles afforded the 1,1′-disubstituted compounds **6** and the 1,2-disubstituted compounds **7** with high regioselectivity (**6**:**7** > 90:10), see Table 1.

We believe that the observed selectivity could be stereocontrolled and due to a directing effect exerted by the boat conformation of the piperazine. The size of the piperazine ring chelating the lithium atom with its bulky *tert*-butyl group in the intermediate **3** tends to force the lithium closer to the unsubstituted cyclopentadienyl ring, producing selectively the complex **4** preferentially to **5**. An electronic effect due to the repulsion by the negative charge on oxygen cannot be ruled out; however, the use of piperidine instead of *N*-methylpiperazine leads to a complicated mixture of substituted ferrocenes in low yield.

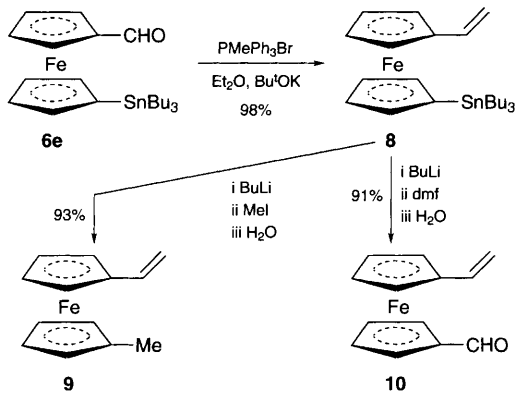
The synthetic value of this method can be illustrated by the use of Bu_3SnCl as electrophile yielding **6e** as a stable, and essentially pure feedstock for further syntheses. Working on a 5 g scale of starting ferrocene-carbaldehyde, 6.6 g of **6e** (13.1 mmol, 56 %) were obtained after usual work up and purification. This compound gave us an efficient and easy access to different ferrocenyl compounds such as **8**, **9** and **10** (Scheme 2).

We have discovered an efficient method for the preparation of unsymmetrical 1,1′-disubstituted ferrocenes by a one-pot procedure, starting from commercially available and inexpensive ferrocenecarbaldehyde. This procedure complements existing methodology[3,4,14] and provides a useful alternative synthetic method to introduce different functionalities on the two

Table 1 Functionalization of ferrocenecarbaldehyde

Entry	Electrophile	Product[a]	Yield[b] (%)	**6**:**7**
a	MeI	R–Me[c]	66	90:10
b	EtI	R–Et	44	90:10
c	Bu^{n}I	R–Bu^n	< 5	—
d	Me_3SiCl	R–$SiMe_3$	69	90:10
e	Bu_3SnCl	R–$SnBu_3$[c]	56	96:4
f	Ph_2PCl	R–PPh_2[c]	22	—
g	BCl_3	R–$B(OH)_2$	21–48	92:8
h	$C_2H_4I_2$	R–I	50	92:8
i	dmf	R–CHO[c]	17	90:10

[a] R is $(OHCC_5H_4)Fe(C_5H_4)$. [b] **6** + **7**. [c] Identical ^{1}H NMR spectra as for authentic compounds.[3,4,12,13] 1,3-Disubstituted or polysubstituted compounds were not detected. In addition, the separation of the two regioisomers **6** and **7** by flash chromatography permits easy access to various 1′-substituted ferrocenecarbaldehydes as pure regioisomers.



Scheme 2

cyclopentadienyl rings of ferrocene. It allows the design and synthesis of potentially useful new ferrocene-based materials. Further work in this area is in progress.

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Footnote

† *General procedure*: 1.5 ml (2.55 mmol) of a *tert*-butyllithium solution (1.7 mol dm^{-3} in pentane) was added dropwise to a solution of 0.29 g (2.9 mmol) of *N*-methylpiperazine in 5 ml of anhydrous thf in a Schlenk tube under argon at room temp. The resulting solution was stirred for 15 min then 0.5 g (2.33 mmol) of ferrocenecarbaldehyde in 5 ml of anhydrous thf was added. After being stirred at room temp. for 2 h, the mixture was cooled to 0 °C and 1.7 ml (2.9 mmol, 1.25 equiv.) of a *tert*-butyllithium solution (1.7 mol dm^{-3} in pentane) was added. The solution was kept at 0 °C for 1 h and then cooled to −78 °C. Various electrophiles (9.3 mmol, 4 equiv.) were added by syringe. The solution was stirred at −78 °C for 30 min, then at room temp. for 0.5–12 h. After hydrolysis and extraction with dichloromethane, the products were purified by flash chromatography on silica gel (pentane–diethyl ether). All compounds gave satisfactory spectroscopic and analytical data.

Selected physical data: **6b**: ^{1}H NMR ($CDCl_3$): δ 9.92 (1H, s), 4.71 (2H, m), 4.55 (2H, m), 4.16 (4H, br s), 2.31 (2H, q, *J* 7.5 Hz), 1.19 (3H, t, *J* 7.5 Hz). GCMS: 242 (100%). **6d**: ^{1}H NMR ($CDCl_3$): δ 9.92 (1H, s), 4.73 (2H, m), 4.53 (2H, m), 4.43 (2H, m), 4.14 (2H, m), 0.22 (9H, s). GCMS: 286 (100%). **6g**: ^{1}H NMR ($CDCl_3$): δ 9.91 (1H, s), 4.76 (2H, m), 4.59 (4H, m), 4.54 (2H, m). **6h**: ^{1}H NMR ($CDCl_3$): δ 9.99 (1H, s), 4.75 (2H, m), 4.56 (2H, m), 4.46 (2H, m), 4.23 (2H, m). GCMS : 340 (45%) **8** was synthesized in diethyl ether using a modification of the literature procedure.[15] ^{1}H NMR ($CDCl_3$): δ 6.41 (1H, dd, *J* 17.5, 10.7 Hz), 5.29 (1H, dd, *J* 17.5, 1.5 Hz), 4.99 (1H, dd, *J* 10.7, 1.5 Hz), 4.25 (2H, m), 4.23 (2H, m), 4.10 (2H, m), 3.90 (2H, m), 1.55 (6H, m), 1.35 (6H, m), 0.8–1.3 (15H, m). GCMS: 502 (20%), 500 (15%). **9** was synthesized by a literature procedure.[3] ^{1}H NMR ($CDCl_3$): δ 9.88 (1H, s) 6.33 (1H, dd, *J* 17.5, 10.7 Hz), 5.37 (1H, d, *J* 17.5 Hz), 5.12 (1H, d, *J* 10.7 Hz), 4.70 (2H, m), 4.53 (2H, m), 4.44 (2H, m), 4.30 (2H, m). GCMS: 240 (100%). **10** was synthesized in the same manner as 1′-vinylferrocenecarbaldehyde, using MeI as electrophile. ^{1}H NMR ($CDCl_3$): δ 6.40 (1H, dd, *J* 17.5, 10.7 Hz), 5.30 (1H, dd, *J* 17.5, 1.5 Hz), 5.04 (1H, dd, *J* 10.7 and 1.5 Hz), 4.25 (2H, t, *J* 1.7 Hz), 4.15 (2H, t, *J* 1.7 Hz), 3.97 (4H, br s), 1.91 (3H, s). GCMS: 226 (100%).

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