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O-Methylephedrine: a highly efficient *ortho*-directing group in the synthesis of enantiopure 1,2-disubstituted ferrocene derivatives

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Abstract

ortho-Lithiation of *N*-ferrocenylmethyl-*O*-methylephedrine (98% d.e.) and reaction with electrophiles followed by nucleophilic replacement of the chiral auxiliary *O*-methylephedrine leads to 1,2-disubstituted enantiopure ferrocenyl derivatives.

Enantiopure ferrocene derivatives are very successfully applied as ligands of homogeneous catalysts, both on the small as well as on the large industrial scale.[1,2] Most ferrocenyl ligands in use are derivatives of commercially available (*S*)- or (*R*)-1-(*N*,*N*-dimethylamino)ethylferrocene (Ugi's amine[3]). Typically, *ortho*-lithiation followed by quenching with an electrophile leads to 1,2-disubstituted intermediates (d.e. $\geq$92%) which can then be further modified by e.g. nucleophilic substitution of the dimethylamino group.[4] With use of this protocol hundreds of bifunctional catalyst ligands have been prepared, all having a ferrocenylethyl backbone.[5]

Much less attention has been paid to the analogous ferrocene derivatives based on a ferrocenylmethyl backbone, mainly since practicable methods for the synthesis of their enantiomerically pure precursors have been described only recently. In addition to traditional resolutions,[4,6] several methods for the asymmetric synthesis of related enantiomerically enriched 1,2-disubstituted ferrocenes have been reported, including cyclopalladation of dimethylaminomethyl ferrocene,[7] *ortho*-metallation of ferrocenyl sulfoxides, dioxanes,[8] amines,[9] amides,[10] phosphineoxides,[11] ferrocenyl oxazolines,[12] ferrocenylhydrazones,[13] azepines[14] or methoxymethyl-pyrrolidine.[15] While the course of lithiation of Ugi's amine is directed by the configuration of the stereogenic center, in the case of the related ferrocenylmethyl derivatives a chiral auxiliary is required.

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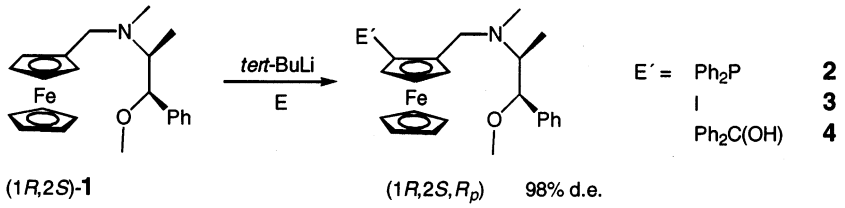
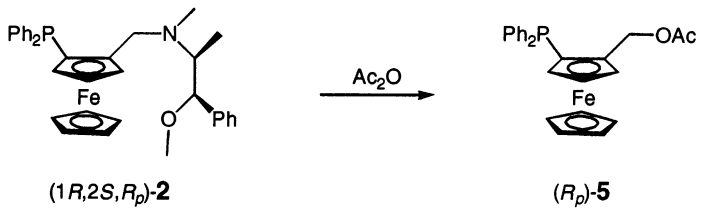
Herein, we describe a very efficient route to 1,2-disubstituted enantiopure ferrocene derivatives involving the use of *O*-methylephedrine as the chiral auxiliary. *O*-Methylephedrine[16] is accessible in one simple step from ephedrine, which is commercially available for a low price in both enantiomeric forms. (1*R*,2*S*)-*O*-Methylephedrine was reacted in CH_3CN with *N*-ferrocenylmethyl-*N*,*N*,*N*-trimethylammonium iodide[17] ($[FcCH_2N(CH_3)_3]I$) giving *N*-ferrocenylmethyl-*O*-methylephedrine, **1**,[†] in 88% yield. *ortho*-Lithiation of **1** with *tert*-BuLi in pentane[‡] followed by addition of an electrophile (E = Ph_2PCl, I_2, $Ph_2C{=}O$) yielded 1,2-disubstituted ferrocenylmethyl derivatives **2**–**4** in reasonable to high yields (**2**, 90%; **3**, 84%; **4**, 64%) and 98% d.e. (Scheme 1), as established by ^1H (**2**–**4**) and ^{31}P NMR (**2**[‡]). (*R*)-configuration at the ferrocene unit was determined via chemical correlation (see below).



Scheme 1.

The major diastereomers of **2** were chosen to show that the chiral auxiliary can be easily replaced. Reaction of **2** with acetic anhydride led to the already known acetate **5**[15] (Scheme 2).



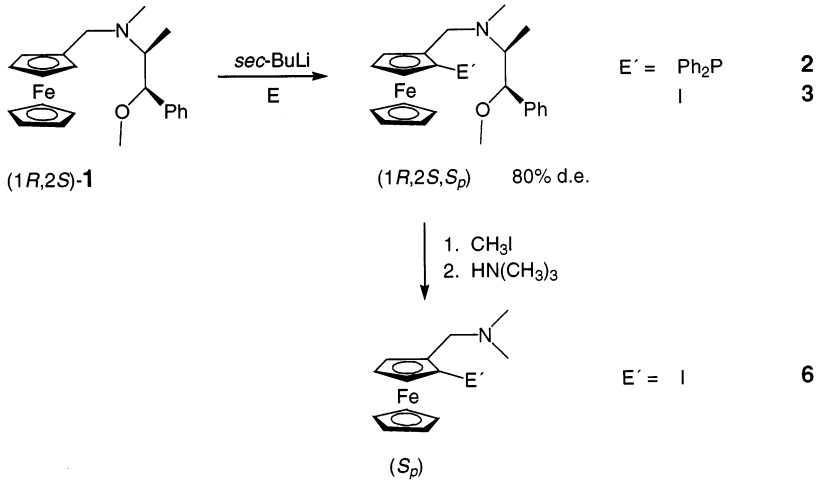
Scheme 2.

The *ortho*-lithiation of **1** not only depends strongly on the temperature but also on the solvent and lithiation reagent. With use of *tert*-BuLi in Et_2O instead of pentane and I_2 as the electrophile, the diastereoselectivity dropped to 86%. Reaction of **1** with *sec*-BuLi and I_2 in

[†] Selected data for (1*R*,2*S*)-**1**: ^1H NMR (400 MHz, $CDCl_3$): δ 1.00 (d, J=6.7 Hz, 3H), 2.25 (s, 3H), 2.82 (dq, J_1=4.7 Hz, J_2=6.7 Hz, 1H), 3.25 (s, 3H), 3.40 (d, J=13.1 Hz, 1H), 3.49 (d, J=13.1 Hz, 1H), 4.05–4.08 (m, 4H), 4.09 (s, 5H), 4.26 (d, J=4.7 Hz, 1H), 7.21–7.35 (m, 5H); $[\alpha]_D^{20}=-71.4$ (c=2, CH_2Cl_2).

[‡] Typical procedure for the *ortho*-lithiation of **1** and for the preparation of **2**: A Schlenk tube is charged with (1*R*,2*S*)-**1** (377 mg, 1 mmol) and 10 ml of dry pentane. To the stirred and degassed solution is added at −78°C under Ar 0.7 ml (1.2 mmol) of *tert*-BuLi (1.7 M in pentane). Stirring is continued for 1.5 hours at −78°C and for additional 2.5 hours at −30°C leading to the formation of an orange precipitate. The suspension is again cooled to −78°C and 1.2 mmol of freshly distilled neat Ph_2PCl (220 mg, 1.2 mmol) is added. The reaction mixture is allowed to warm up to room temperature and is stirred for additional 16 hours. After quenching with a saturated aqueous $NaHCO_3$ solution the organic phase is washed with brine, dried with $MgSO_4$ and the solvent is removed under reduced pressure. The residue is purified by chromatography on silica (PE:Ac_2O 95:5). Yield 90%, d.e. 98%. Selected data for (1*R*,2*S*,R_p)-**2**: ^1H NMR (400 MHz, $CDCl_3$): δ 0.79 (d, J=6.8 Hz, 3H), 2.01 (s, 3H), 2.75 (dq, J_1=3.8 Hz, J_2=6.8 Hz, 1H), 3.22 (s, 3H), 3.44 (d, J=13.5 Hz, 1H), 3.73 (s, 1H), 3.79 (d, J=13.5 Hz, 1H), 3.94 (s, 5H), 4.18 (s, 2H), 4.29 (bs, 1H), 7.15–7.4 (m, 15H). ^{31}P NMR (162 MHz, $CDCl_3$): δ −22.00. $[\alpha]_D^{20}=+213.7$ (c=1, CH_2Cl_2).

pentane gave product **3** in only 79% d.e., however, a spectacular change in diastereoselectivity was seen when Et_2O[§] instead of pentane was used as the solvent (Scheme 3). After quenching with Ph_2PCl or I_2 products **2**[§] and **3** were both isolated in 80% d.e., but with the major diastereomer now having (S_p) configuration at the ferrocene unit.



Scheme 3.

This assignment was determined by transforming **3** into 2-iodo-1-dimethylaminomethylferrocene, **6**, of known absolute configuration[6] (Scheme 3), a reaction which also shows that the chiral auxiliary can be replaced easily by other nucleophiles.

In conclusion, we have invented *O*-methylephedrine as a chiral auxiliary which directs lithiations of ferrocene in either *ortho*-position depending on lithiation reagent and solvent used. (1*R*,2*S*)-*N*-Ferrocenylmethyl-*O*-methylephedrine reacts with *tert*-BuLi in pentane to give the corresponding (S_p)-lithioferrocene with 98% d.e., while with *sec*-BuLi in Et_2O lithiated product with (R_p) configuration and a diasteroselectivity of 80% is obtained.

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[§] The same experimental procedure as described above, except that diethyl ether is used as the solvent and *sec*-BuLi as the lithiation agent. Selected data for (1*R*,2*S*,S_p)-**2**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.69 (d, J=6.8 Hz, 3H), 2.05 (s, 3H), 2.67 (dq, J_1=3.0 Hz, J_2=6.8 Hz, 1H), 3.05 (s, 3H), 3.45 (d, J=13.0 Hz, 1H), 3.75 (t, J=1.1 Hz, 1H), 3.79 (dd, J_1=13.0 Hz, J_2=2.3 Hz, 1H), 3.92 (d, J=3.0 Hz, 1H), 3.95 (s, 5H), 4.22 (t, J=2.4 Hz, 1H), 4.47 (bs, 1H), 7.1–7.4 (m, 15H); ^{31}P NMR (162 MHz, $CDCl_3$): δ –22.12.

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