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Synthesis of new ferrocenyl-containing tertiary alcohols, analogs of L-prolinol-based organocatalysts

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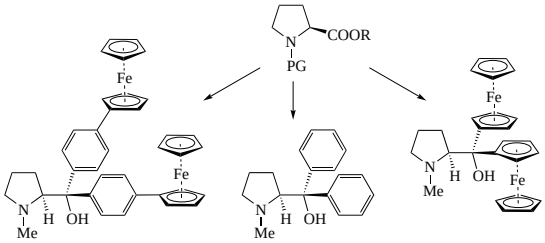
Syntheses of new ferrocenyl-containing tertiary alcohols derived from L-proline were developed. In these alcohols, two ferrocenyl groups are bonded at prolinol moiety directly or through *p*-phenylene spacer. Specific features for the ferrocene Grignard reagents were discovered.

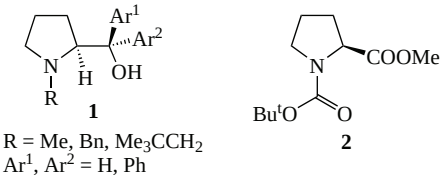


Keywords: asymmetric organocatalysis, ferrocene, proline, *tert*-butoxycarbonyl protective group, ferrocenylmagnesium bromide, chiral tertiary alcohols, X-ray molecular structure.

Much attention is attracted now to organocatalysis,[1,2] one of vectors being the use of L-proline derivatives[3–6] effective in asymmetric aldol,[7–9] Michael,[10] Mannich[11] condensations, cycloaddition and reduction reactions.[12] Immobilized proline derivatives have been successfully employed as recyclable organocatalysts.[13,14] Previously syntheses of L-prolinol derivatives of type **1** were reported,[15] which were tested as chiral catalysts in reactions of diethylzinc with aromatic aldehydes. The ability of compounds **1** to stereoselectively afford the products, depends strongly on the nature of R, Ar^1 and Ar^2. In the case of R = Me, $Ar^1 = Ar^2$ = Ph, high selectivity was demonstrated. Otherwise, if R = Me, $Ar^1 = Ar^2$ = H, no selectivity was observed.[15]

Phenyl and ferrocenyl groups differ in both effective size (a distance between two Cp-rings in ferrocene is 3.3 Å[16]) and electronic properties (ferrocenyl group exhibits electron donating properties[17]). Therefore, it seems reasonable to prepare ferrocenyl analogs of structure **1** (Ar^1 and Ar^2 are ferrocene-containing moieties) and to compare stereoselectivity of phenyl and ferrocenyl derivatives. Owing to large effective size of ferrocenyl group, good selectivity may be anticipated.

In this paper, we report on synthesis of new L-prolinol derivative with two ferrocenyl groups located close to chiral center of L-prolinol fragment like phenyl groups in structures **1**. We also synthesized analog of **1**, in which L-prolinol moiety is connected with ferrocenyl through *p*-phenylene spacer. This spacer decreases steric effect of ferrocenyl moiety while being a good conductor of electronic effects. Starting material for the synthesis of tertiary alcohols was readily available[18] *N*-protected *N*-*tert*-butoxycarbonyl-L-proline methyl ester **2**. Since molecule **2** contains carbamoyl protective group, for its transformation into tertiary prolinols we used organomagnesium rather than more reactive organolithium reagents in the corresponding reactions. Attempts to use benzyl or allyl protective groups did not provide satisfactory results at the Grignard addition step.



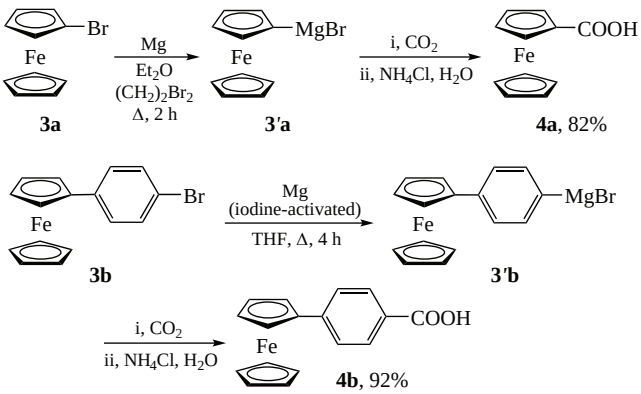
1

R = Me, Bn, Me_3CCH_2

Ar^1, Ar^2 = H, Ph

2

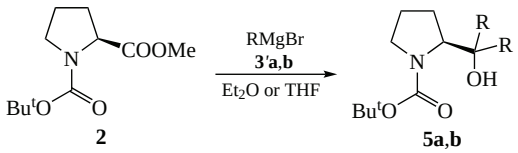
Several remarks about preparation of organomagnesium compounds in our case should be made. The reaction of bromoferrocene **3a** with magnesium in diethyl ether and in THF does not start *per se* and also after preliminary activation with iodine. We found, however, that gradual addition of a diethyl ether solution of bromoferrocene **3a** and 1,2-dibromoethane in 1 : 2 molar ratio to excess of magnesium in diethyl ether would successfully produce ferrocenylmagnesium bromide **3′a** since high yield of ferrocenecarboxylic acid **4a** was achieved upon treatment with CO_2 (Scheme 1). The reaction of 4-bromophenylferrocene **3b** with magnesium under the same conditions



Scheme 1

leads to replacement of bromine for hydrogen to give phenylferrocene, possibly *via* a radical process, which is in agreement with the previously published data.[19] Luckily, if iodine is used for activation of magnesium, 4-ferrocenylphenylmagnesium bromide **3′b** is formed since the corresponding carboxylic acid **4b** is obtained in 92% yield.

tert-Butoxycarbonyl protecting group permits to prepare alcohols **5a** and **5b** in good yields by the reaction of ester **2** with 2.05–2.30 equiv. of organomagnesium compounds **3′a** or **3′b**, respectively (Scheme 2). Formation of monoferrocenyl compounds in trace amounts was also observed in both cases.



2 **5a**,**b**

a R = Fc, 60%
b R = 4-FcC$_6$H$_4$, 85%
Fc is ferrocenyl

Scheme 2

Crystal and molecular structures of compounds **5a** and **5b** were determined (Figures 1 and 2).† Both compounds **5a** and **5b** crystallize in chiral space group $P2_1$. In these structures, chiral carbon atoms possess *S*-configuration and the Flack parameters are equal to zero within experimental errors [0.00(1) and 0.00(2)]. In both structures, central pyrrolidine cycles adopt 'envelope' conformation. In **5a**, methylene C(3) carbon [lying in β-positions to both N(1) and prolinol C(1) atoms] acts as an 'envelope flap' with 0.47 Å deviation (towards Fc substituent) from the least-squares plane of other four ring atoms. In contrast, in molecule **5b** methylene C(2) carbon [lying in α-position to proline C(1) atom] serves as an 'envelope flap' with 0.45 Å deviation (opposite to Fc substituent) from the base plane of other four ring atoms. In both cases, nitrogen atoms adopt almost planar configuration with C–N–C angles ranging within 113.6(1)–122.6(3)° due to sp^2-hybridization of carboxylate C atoms. Of interest, among C–N–C angles,

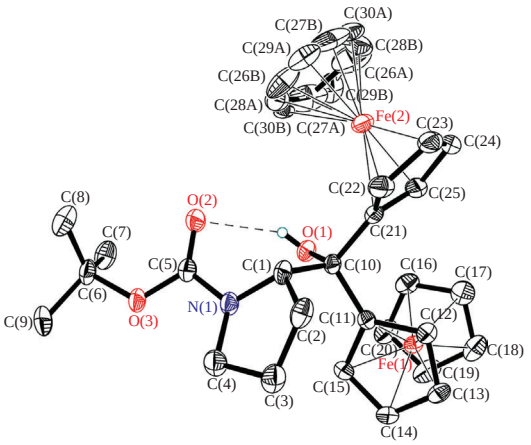


Figure 1 Molecular structure of *tert*-butoxycarbonyl-protected prolinol **5a**. Thermal ellipsoids are shown at 50% probability level. Fe–C bonds are depicted by thin lines. Dashed line is used for hydrogen bond. Minor component of disorder is drawn by open lines.

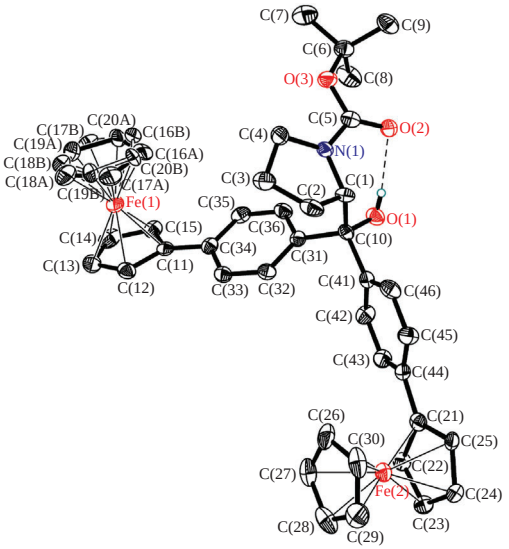


Figure 2 Molecular structure of *tert*-butoxycarbonyl-protected prolinol **5b**. Thermal ellipsoids are shown at 50% probability level. Fe–C bonds are depicted by thin lines. Dashed line is used for hydrogen bond. Minor component of disorder is drawn by open lines.

endocyclic values are the smallest. In both structures, *N*-carbonyl substituents are almost coplanar with pyrrolidine rings since O=C–N–C torsion angles are less than 18°. Shortened bond lengths O_2C–N [1.344(5) Å for **5b**; 1.362(2) Å for **5a**] also prove the presence of significant conjugation. Other C–C, C–O, and C–N bond lengths exhibit ordinary values for organic compounds. As expected, all cyclopentadienyl rings are planar and all Fe–C bonds represent typical lengths [1.98(2)–2.08(2) Å]. In prolinols **5a**,**b**, one of four Cp-rings is rotationally (around Fe–Cp$_{cent}$ line) disordered with occupancy ratios of 0.63(2)/0.37(2) and 0.64(1)/0.36(1), respectively. Additionally, in **5a**,**b** moderate intramolecular hydrogen bonds O(1)–H···O(2) [O···O separations of 2.655(4) and 2.803(2) Å] were observed. No short intermolecular interactions were found in the studied structures.

Target *N*-methylprolinols **6a**,**b** were synthesized by reduction of carbamates **5a**,**b** with $LiAlH_4$ (Scheme 3). Compound **6a** would easily decompose in acidic media producing diferrocenyl ketone. Such decomposition also takes place during chromatographic purification on silica gel. In order to prepare alcohol **6a** in a pure state, flash chromatography must be used.

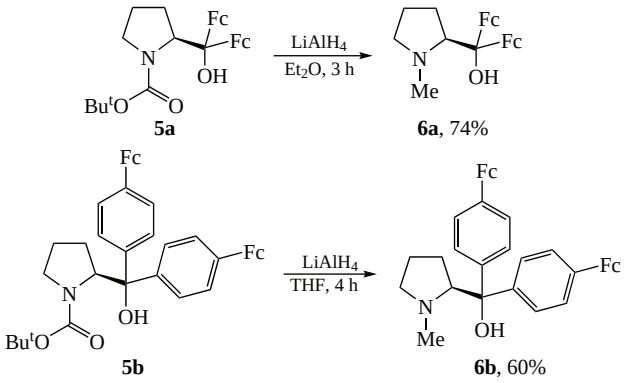
In conclusion, new chiral ferrocene-containing tertiary alcohols of L-prolinol series were prepared. Catalytic properties

† *Crystal data for* **5a**. $C_{30}H_{35}Fe_2N_1O_3$, F_w = 569.29, monoclinic, a = 7.3565(1), b = 9.4157(2) and c = 18.5633(4) Å, β = 90.8560(7)°, V = 1285.67(4) Å^3, space group $P2_1$, Z = 2, d_{calc} = 1.471 g cm^{-3}, $F(000)$ = 596, μ(MoK_α) = 1.161 mm^{-1}, orange prism with dimensions *ca.* 0.45 × 0.45 × 0.20. Total 21483 reflections (6146 unique, R_{int} = 0.0194). Carbon H atoms were placed in calculated positions and refined using a riding model. Hydroxy H atom was found from difference Fourier map and refined isotropically. The final residuals were: R_1 = 0.0235 for 6024 reflections with $I > 2\sigma(I)$ and wR_2 = 0.0624 for all data and 378 parameters. Flack parameter 0.00(1). GoF = 1.029.

Crystal data for **5b**. $C_{42}H_{43}Fe_2N_1O_3$, F_w = 721.47, monoclinic, a = 15.2858(8), b = 7.5040(3) and c = 16.1888(6) Å, β = 111.637(2)°, V = 1726.09(13) Å^3, space group $P2_1$, Z = 2, d_{calc} = 1.388 g cm^{-3}, $F(000)$ = 756, μ(MoK_α) = 0.881 mm^{-1}, orange needle with dimensions *ca.* 0.43 × 0.06 × 0.01. Total 17473 reflections (6033 unique, R_{int} = 0.0591). Carbon H atoms were placed in calculated positions and refined using a riding model. Hydroxy H atom was found from difference Fourier map and refined isotropically. The final residuals were: R_1 = 0.0452 for 4783 reflections with $I > 2\sigma(I)$ and wR_2 = 0.0668 for all data and 486 parameters. Flack parameter 0.00(2). GoF = 1.033.

Data were collected on Bruker SMART APEX II diffractometer using graphite monochromatized MoK_α radiation (λ = 0.71073 Å) at 150 K. The structures were solved by direct methods and refined by full-matrix least-squares on F^2 for all non-hydrogen atoms.

CCDC 2211904 (**5a**) and 2211906 (**5b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* https://www.ccdc.cam.ac.uk.



Scheme 3

of synthesized compounds will be described in the following paper together with properties of analogous secondary alcohols.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.01.019.

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