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Mendeleev Commun., 2024, **34**, 201–203

Mendeleev Communications

Synthesis, structure and catalytic activity of new ferrocenyl-containing secondary alcohols derived from L-proline

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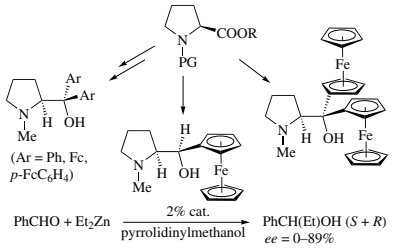
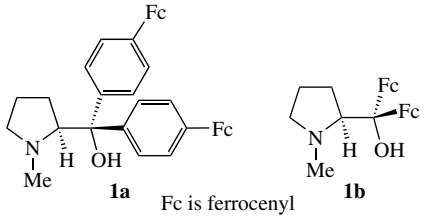
DOI: 10.1016/j.mencom.2024.02.013

New ferrocenyl-containing diastereomeric secondary alcohols derived from L-proline of (ferrocenyl)(pyrrolidin-2-yl)methanol chemotype were synthesized. Their crystal and molecular structure was explored. The prepared chiral secondary and tertiary alcohols in which hydroxy group is sterically hindered by ferrocene substituents show asymmetric induction effect in reaction between diethylzinc and benzaldehyde.

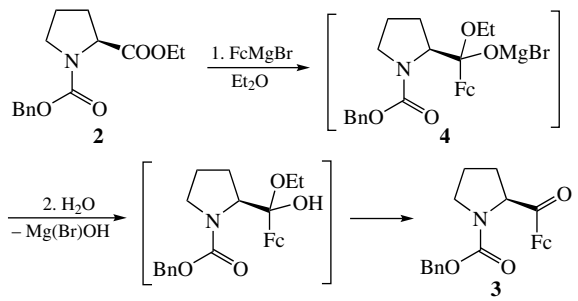


Keywords: asymmetric organocatalysis, ferrocene, proline, benzyloxycarbonyl protective group, ferrocenylmagnesium bromide, chiral secondary alcohols, X-ray molecular structure, enantioselective addition, diethylzinc.

In last two decades many reports dealing with asymmetric catalysis by L-proline and its derivatives were published.[1–12] In this regard, it is important to introduce new compounds based on L-proline. In the previous paper,[13] we described the preparation of ferrocenyl-containing tertiary alcohols **1a**,**b** derived from L-proline. In the present paper we report on synthesis of the analogous secondary alcohols and on catalytic properties of alcohols of both types.

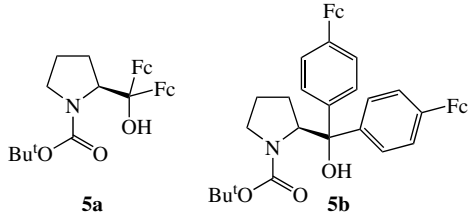


The starting material for the synthesis of secondary alcohols was readily available[14] *N*-protected ester **2**. We prepared ferrocenyl ketone **3** by the action of ferrocenylmagnesium bromide on ester **2** (Scheme 1). In this reaction, formation of the regular tertiary diferrocenylmethanols was also observed; however, if an excess of ferrocenylmagnesium bromide in diethyl ether at 0 °C was used, the yield of desired monoferrocenyl ketone **3** remained at 30% level. We propose that ketone **3** in this reaction arises due to stability of intermediate alkoholate **4** which would precipitate. After an action of water, this alkoholate transforms into ketone **3** (see Scheme 1).



Scheme 1

Molecular structure of product **3** was established by X-ray diffractometry (Figure 1).† It crystallizes in chiral space group $P2_12_12_1$ with Flack parameter equal to 0.001(7) for the studied sample. Main geometric features of proline fragment in ketone **3** are close to those found for previously synthesized[13] compounds **5a** and **5b**. In contrast to both **5a**,**b**, ferrocenyl substituent is completely ordered with Fe–Cp_{cent} separations equal to 1.636(3) and 1.648(3) Å.



† *Crystal data for* **3**. $C_{23}H_{23}Fe_1N_1O_3$, $M = 417.27$, orthorhombic, $a = 8.1224(5)$, $b = 12.0383(7)$ and $c = 19.5619(12)$ Å, $V = 1912.8(2)$ Å^3, space group $P2_12_12_1$, $Z = 4$, $d_{calc} = 1.449$ g cm^{-3}, $F(000) = 872$, $\mu(MoK_\alpha) = 0.813$ mm^{-1}, orange prism with dimensions *ca.* 0.45×0.35×0.20 mm. Total 23158 reflections (5089 unique, $R_{int} = 0.0414$). All H atoms were found from difference Fourier map and refined isotropically. The final residuals were: $R_1 = 0.0349$ for 4709 reflections with $I > 2\sigma(I)$ and $wR_2 = 0.0743$ for all data and 345 parameters. Flack parameter 0.001(7). GoF = 1.048. Data were collected on Bruker SMART Photon II machine using graphite monochromatized MoK_α radiation ($\lambda = 0.71073$ Å) at 150 K. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 for all non-hydrogen atoms.

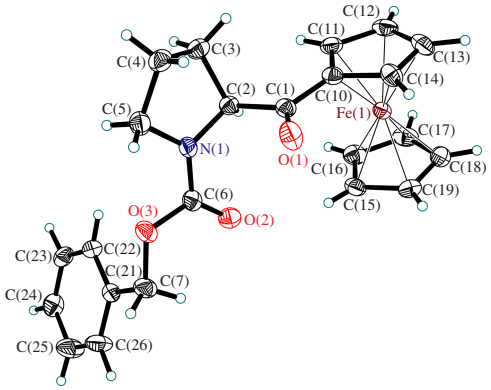
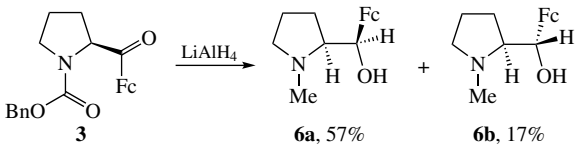


Figure 1 Molecular structure of ketone **3**. Thermal ellipsoids are shown at 50% probability level. Fe–C bonds are depicted by thin lines.

Reduction of ketone **3** gives two diastereomeric alcohols **6a**,**b** separable by chromatography (Scheme 2). The selectivity of this reaction (**6a**/**6b** = 3 : 1 in reaction mixture) is in agreement with the prediction of the Cram chelation model.

Structures of both these stereoisomers were unambiguously established by X-ray diffraction techniques (Figures 2 and 3).[†] Compounds **6a** and **6b** crystallize in chiral space groups $P2_12_12_1$ and $P2_1$, respectively, the Flack parameters are close to zero [–0.012(6) and 0.02(1)]. In both cases, asymmetric units contain two independent molecules with very close geometric parameters (for orthogonal fitting of independent molecules, see Online Supplementary Materials, Figure S1). The C–C, C–N, and C–O bond lengths are of ordinary values for organic compounds.



3 **6a**, 57% **6b**, 17%

Scheme 2

Crystal data for **6a**. $C_{16}H_{21}Fe_1N_1O_1$, M = 299.19, orthorhombic, a = 10.0889(6), b = 12.9035(8) and c = 22.4461(13) Å, V = 2922.1(3) Å^3, space group $P2_12_12_1$, Z = 8, d_{calc} = 1.360 g cm^{-3}, $F(000)$ = 1264, μ(MoK_α) = 1.024 mm^{-1}, orange prism with dimensions *ca.* 0.35×0.20×0.07 mm. Total 57221 reflections (8510 unique, R_{int} = 0.0557). Hydroxy H atom was found from difference Fourier map and refined isotropically, all others were placed in calculated position and refined using a riding model. The final residuals were: R_1 = 0.0303 for 7768 reflections with $I > 2\sigma(I)$ and wR_2 = 0.0674 for all data and 345 parameters. Flack parameter –0.012(6). GoF = 1.033. Data were collected on Bruker SMART APEX II diffractometer using graphite monochromatized MoK_α radiation (λ = 0.71073 Å) at 100 K. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 for all non-hydrogen atoms.

Crystal data for **6b**. $C_{16}H_{21}Fe_1N_1O_1$, M= 299.19, monoclinic, a = 9.8670(4), b = 13.5433(6) and c = 10.5297(5) Å, β = 99.3548(18)°, V = 1388.39(11) Å^3, space group $P2_1$, Z = 4, d_{calc} = 1.431 g cm^{-3}, $F(000)$ = 632, μ(MoK_α) = 1.077 mm^{-1}, orange prism with dimensions *ca.* 0.35×0.10×0.05 mm. Total 25938 reflections (6670 unique, R_{int} = 0.0472). 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 = 0.0448 for 6425 reflections with $I > 2\sigma(I)$ and wR_2 = 0.1127 for all data and 486 parameters. Flack parameter 0.017(12). GoF = 1.052. Data were collected on Bruker SMART APEX II diffractometer using graphite monochromatized MoK_α radiation (λ = 0.71073 Å) at 100 K. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 for all non-hydrogen atoms.

CCDC 2211905 (**3**), 2266192 (**6a**) and 2266191 (**6b**) 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.

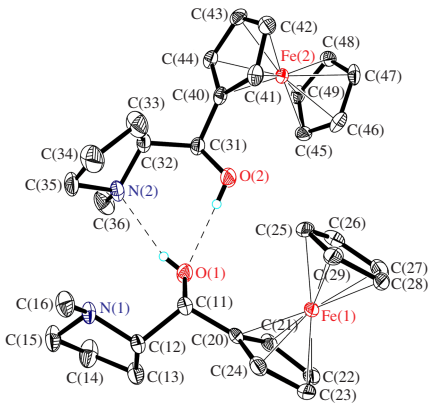


Figure 2 Molecular structure of diastereomer **6a**. Thermal ellipsoids are shown at 50% probability level. Fe–C bonds are depicted by thin lines. Dashed lines are used for hydrogen bonds.

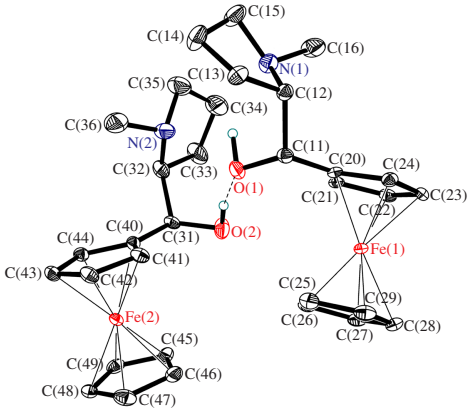
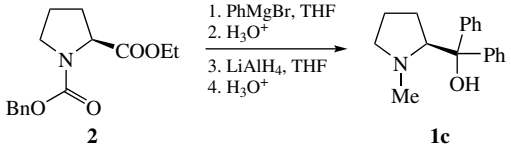


Figure 3 Molecular structure of diastereomer **6b**. Thermal ellipsoids are shown at 50% probability level. Fe–C bonds are depicted by thin lines. Dashed line is used for hydrogen bond.

The Fe–C distances vary within 2.034(5)–2.064(5) Å for both isomers. All nitrogen atoms possess tetrahedral configuration with C–N–C angles ranging within 103.6(2)–113.3(4)°. In both structures, central pyrrolidine cycles adopt 'envelope' conformation with N or C_α atoms occupying 'envelope flap' positions. In both compounds **6a** and **6b**, pairs of crystallographically independent molecules are combined in dimers by moderate O–H···O and O–H···N hydrogen bonds; ferrocenyl substituent is completely ordered with Fe–Cp_{cent} separations range within 1.644–1.651 Å.

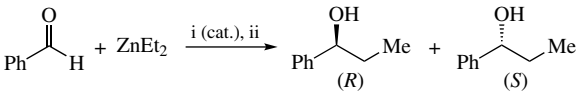
For comparison with the above ferrocenyl derivatives, an already known[15] phenyl analog **1c** was also prepared (Scheme 3).

Tertiary amino alcohols are successfully used as organocatalysts in addition of organozinc compounds to carbonyl group.[16] In this study, catalytic properties of prolinols **1a**–**c** and **6a**,**b** in reaction of benzaldehyde with diethylzinc were examined (Scheme 4). The reactions were performed at 0 °C in hexane–toluene 2 : 1 mixture using 2 mol% of the catalyst for 24 h. Earlier[15] it was found that the Bu^{n}Li additive could improve the enantioselectivity; however, we carried out our experiments in the absence of Bu^{n}Li. The products were isolated by column chromatography, and thus the catalysts were easily recovered. Enantiomeric excesses were determined by chiral HPLC.



2 **1c**

Scheme 3



Catalyst	*ee* (%)	Catalyst	*ee* (%)
1a	0	**6a**	47 (*R*)
1b	76 (*S*)	**6b**	0
1c	89 (*S*)		

Scheme 4 *Reagents and conditions:* i, $PhCHO/Et_2Zn$/catalyst molar ratio is 1:2.2:0.02, PhMe–hexane (1:2), 0 °C, 24 h; ii, HCl, H_2O.

Configuration of an asymmetric atom was established by comparison of the data with those estimated earlier for known substances (see Scheme 4).

In our experiments (see Scheme 4) the stereoinduction of compound **1c** appeared to be lower than previously reported.[15] This can be explained by different solvent systems used in both cases. The introduction of ferrocenyl groups into phenyl rings (catalyst **1b**) does not affect essentially on stereoselectivity. Surprisingly, the persence of two ferrocenyl groups in **1a**, instead of phenyl ones in **1c**, results in complete loss of selectivity. We propose that in this case transition state including the catalyst should be too hindered and cannot be achieved, and the reaction proceeds without participation of the catalyst. Replacement of one ferrocenyl group in **1a** with hydrogen atom leads to appearance of enantioselectivity in the case of **6a** (but not **6b**). This fact is in accord with activity of phenyl analogs of **6a** and **6b**.[15]

In conclusion, new chiral ferrocenyl derivatives of L-prolinol were synthesized. Their stereo-differentiating activity as organocatalysts was tested in the reaction of benzaldehyde with diethylzinc. Some of ferrocenyl derivatives provide reasonable enantioselectivity, however it is lower than in the case of phenyl analog. So, steric hindrance caused by the presence of bulky ferrocenyl group in these cases does not lead to an increase in enantioselectivity contrary to our expectations. Nonetheless, now the corresponding ferrocene-containing amino alcohols are reliably available for synthesizing according to the developed methods and can be used in further catalytic investigations.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.02.013.

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Received: 13th October 2023; Com. 23/7270