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Synthesis of Novel Ferrocenyl N/O-Heterocycles, Chiral P, N-Ligand and α-dehydro-β-amino acid Derived Short Peptides from Morita-Baylis-Hillman Adducts of Ferrocenealdehyde

Suchithra Madhavan*, Ponnusamy Shanmugam* and Ramavarma Luxmi Varma*
The ‘golden triangle’ of Fe, OH/NH, COO moieties created by classical/aza-MBH reaction of ferrocene-aldehyde has been exploited for the first time to the synthesis of novel multisubstituted ferrocenyl N/O heterocycles, chiral P,N ligand and ferrocenylo-dehydro-β-peptides.

Ferrocene (Fc), the fascinating organometallic sandwich compound and its derivatives have received increasing interest of chemists due to its applications in asymmetric catalysis,1 materials chemistry,2 bio-organometallics3 and medicine.4 The unique structure of ferrocene is responsible for the ubiquity of variety of chiral ferroceny phosphine ligands, one of the most successful classes of ligands in asymmetric catalysis. Development of structurally innovative chiral ferrocene ligands for known asymmetric reactions and/or new applications from these ligands is a thriving area in synthetic organic chemistry. In the quest for novel hemilabile ligands, ferrocenyl pyrrolidines attained special attention which are proven efficient ortho-directing groups leading to the synthesis of chiral ferrocenyl P,N-ligands.5 Substituted dihydrofurans are key structural units in many natural products and also serve as useful synthetic intermediates.6 Hence, synthesis of multi substituted ferrocenyl N/O heterocycles is of high interest which will provide interesting scaffolds for the design of chiral ligands. Furthermore, ferrocene has recently been recognized as a reliable organometallic scaffold for its ability to induce secondary structures and supramolecular arrangements to its peptide conjugates. This bioorganometallic chemistry is envisioned to provide not only a peptidomimetic basis for protein folding, but also pharmacologically useful compounds, artificial receptors, asymmetric catalysts, new materials with functional properties, electrochemical sensor devices and immunoassay reagents.7

Stimulated by the lack of precedents for exploiting the ‘golden triangle’ of Fe, NH/OH, COO of ferrocenyl Morita-Baylis-Hillman (MBH) adducts8 together with our ongoing interest in synthetic applications of MBH adducts9 we embarked upon the synthesis of ferrocenyl N/O heterocycles, chiral P, N-ligand and highly strained metallo β-peptides from MBH adducts of Fe-CHO and the results are presented in this communication.

Synthesis of ferrocenyl N/O heterocycles: The synthetic precursor’s of ferrocenyl heterocycles viz. ferrocenyl MBH adducts 2-7 were prepared8,10 by classical and aza-MBH reaction of Fe-CHO, 1 (Scheme 1).

Initially, ferrocenyl MBH adduct 2 on alkylation with K₂CO₃/allyl bromide afforded N-allylated adduct 8 in 88% yield. Ring closing metathesis (RCM) of 8 in toluene with 10 mol% Grubbs II generation catalyst yielded 2-ferrocenyl-3-cyano-pyrroline 11 in 48% yield. Similarly, ester derivatives of ferrocene appended pyrrolines 12 and 13 were also prepared from MBH adducts 3 and 4 in moderate yields (Scheme 2). On the other hand, the classical MBH adduct 7 underwent O-allylation followed by RCM to yield 2-ferrocenyl-2-cyano-dihydrofuran 16 in 40% yield.11 After the successful synthesis of ferrocenyl pyrroline and dihydrofuran derivatives, next we focussed on the synthesis of ferrocenyl piperidine derivative 14. Gratifyingly, [4+2]-annulation reaction12 of MBH adduct 4 with methyl vinyl ketone in presence of DBU afforded an inseparable diastereomeric mixture of tetrasubstituted ferrocenyl piperidine derivative 14 (dr. 1:0.5) in 78% yield (Scheme 2).

Scheme 2 Synthesis of ferrocenyl N/O heterocycles 11-14 and 16

Synthesis of ferrocenyl P/N ligands: Next, keeping the goal of synthesis of structurally varied chiral ligands in mind, we investigated the directive orthometatilating ability of NTs group attached to the ferrocene backbone of ferrocenyl MBH adducts. To our dismay, the lithiation of N-protected MBH adduct 17 with TMEDA and n-BuLi followed by quenching with phosphinyl chloride afforded the phosphine substituted product 19 instead of the expected acyclic chiral ligand 18 in 92% yield (Scheme 3). N-allyl substitution in the MBH adduct 10 didn’t alter the reaction which also yielded the phosphine substituted product 19 (Table 1, entry 1). Evidently, the rearranged MBH adduct 20 remained unaffected under the lithiation-phosphinylation condition (Table 1, entry 2).

Scheme 3 Attempted synthesis of acyclic chiral ligand 18

Metallation followed by phosphorylation reaction of unprotected MBH adduct 4, afforded rearranged N-phosphinylated product 21 along with 19 (Table1, entry 3). The unprotected rearranged MBH adduct 6 also underwent same sort of reaction resulting into compounds 21 and 19 (Table 1, entry 4). On the basis of the above experiments, we concluded that planarity of Fe stabilises the rearranged product having NH moiety away from the Fe backbone,
hence failed to direct the metallation to ortho position of 
cyclopentadiene ring, which jeopardized our efforts towards 
the synthesis of chiral ferrocenyl ligands. However, the 
method offers novel N-phosphinylated ferrocenyl derivatives 
very good yield.

Table 1 Efforts to synthesise acyclic chiral ligands from 
MBH adducts

<table>
<thead>
<tr>
<th>Entry</th>
<th>MBH adduct</th>
<th>Product (Yield %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. i). TMEDA (1.3 equiv.), n-Bu Li (2.5 equiv.), THF, -78 ºC, 1 h; 

Then we turned our attention towards the ferrocenyl 
hetereocycles, where the N/O pendant responsible for planar 
chiral induction is fixed in the cyclic framework attached to 
the Fe-scaffold. The ferrocene matrix bearing pyrrolidine 
peptide 13 was chosen as the model substrate and its ability 
to undergo diastereoselective ortholithiation-phosphinylation 
was first investigated. Thus, treatment of THF solution of 
the MBH adduct 4 and rearranged adduct 5 under basic 

Synthesis of ferrocenyl-α-dehydro-β-peptides and β-lactam:

α-Dehydro amino acids are important precursors of unnatural 
peptides that are capable to induce β-bends in small peptide 
sequences with enhanced biological activities and selectivity. 

In this scenario, we prepared two types of ferrocenyl 
α-dehydro-β-amino acids 23 and 24 by hydrolysis of the 
ferrocenyl MBH adduct 4 and rearranged adduct 5 under basic 
with acid 24. The structures of chiral ferrocenyl ligand 22 were established 
by spectroscopic (1H NMR, IR and Mass), multinuclear 
(13C(1H), 31P(1H)) and 2D NMR techniques. The 1H NMR 
spectrum clearly showed signals for the unsubstituted 
cyclopentadienyl protons as a singlet for five protons at δ 4.20 ppm and 1.2 disubstituted cyclopentadienyl protons as three mutually coupled multiplets at δ 4.17-4.11, 3.71-3.49 and 3.28-3.19 ppm. Interestingly, the ester methylene protons 
appeared as two well separated multiplets due to the 
interaction with phosphine moiety. The 31P(1H)NMR 
spectrum displayed a resonance at δP -16.17 ppm.

Scheme 5 Synthesis of ferrocenyl amino acids 23 and 24

The α-dehydro-β-amino acid 24 was converted into dipeptide 
26 with glycine ester hydrochloride by solution phase 
coupling reaction using EDC as coupling agent (Scheme 6).

Scheme 6 Synthesis of ferrocenyl short peptide 26

For maximum use the conformational constrain exerted by the dehydro residue, L-proline having a constrained backbone dihedral angle has been utilized to prepare the 

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phosphinic chloride (BOPCl) at room temperature (Table 2, entry 5). Indeed, these simple easy to prepare MBH derived strained ferrocenyl-β-amino acids can be coupled with PNA’s and biogenic peptides like enkephalin and bradykinin analogues for organometallic labelling like Sonogashira and click reaction.  

Table 2 Synthesis of ferrocenyl short peptides 27-29 and β-lactam 30

<table>
<thead>
<tr>
<th>Entry</th>
<th>Fe-amino acid</th>
<th>Amino acid</th>
<th>Dipeptide</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fe HCl.H-(L) Pro-OMe</td>
<td>HCl.H-(L) Pro-OMe</td>
<td>24</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>Fe HCl.H-Gly-OMe</td>
<td>HCl.H-Gly-OMe</td>
<td>23</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>Fe HCl.H-(L) Pro-OMe</td>
<td>HCl.H-(L) Pro-OMe</td>
<td>29</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>Fe HCl.H-(L) Pro-OMe</td>
<td>HCl.H-(L) Pro-OMe</td>
<td>30</td>
<td>86</td>
</tr>
</tbody>
</table>

*amino acid (1 equiv.), EDC.HCl (3 equiv.), HOBt.H₂O (3 equiv.), DIPEA (5 equiv.), DCM: DMF (1:1; 0 °C-rt, 12 h; BOPCl (1.5 equiv.), DIPEA (1.5 equiv.), THF, rt, 12 h.

Conclusions

In conclusion, the synthesis of novel multsubstituted ferrocenyl pyrrolidines, furan and piperidine from MBH adducts of ferrocenealdehyde have been achieved. Ferrocenyl P.N ligand with multiple chirality has been synthesised involving a highly diastereoselective ortholithiation (de >99), adding new class of privileged ligands to the current repertoire. A short synthesis of novel ferrocenyl α-dehydro-β-peptides, a new entry for de novo peptide design has also been reported herein. Efforts to synthesise and study the catalytic activity of analogues ligands from ferrocenyl MBH adducts are in progress.

Acknowledgements

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Notes and references


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