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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†

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The 'golden triangle' of Fc, OH/NH, COO moieties created by classical/aza-MBH reaction of ferrocenealdehyde has been exploited for the first time for the synthesis of novel multisubstituted ferrocenyl N/O heterocycles, chiral P,N ligands and ferrocenyl α-dehydro-β-peptides.

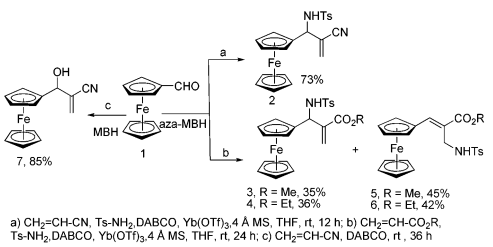
Ferrocene (Fc), the fascinating organometallic sandwich compound and its derivatives have received increasing interest from chemists due to their applications in asymmetric catalysis,[1] materials chemistry,[2] bio-organometallics[3] and medicine.[4] The unique structure of ferrocene is responsible for the wide variety of chiral ferrocenyl 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 Fc, NH/OH, COO moieties of ferrocenyl Morita–Baylis–Hillman (MBH) adducts[8] together with our ongoing interest in synthetic applications of MBH adducts[9] we embarked upon the synthesis of ferrocenyl N/O heterocycles, chiral P,N-ligand and highly strained metallo β-peptides from MBH adducts of Fc-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 prepared[8,10] by classical and aza-MBH reaction of Fc-CHO, **1** (Scheme 1).

Initially, ferrocenyl MBH adduct **2** on alkylation with K_2CO_3/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



a) CH_2=CH-CN, Ts-NH_2, DABCO, Yb(OTf)$_3$, 4 Å MS, THF, rt, 12 h; b) CH_2=CH-CO_2R, Ts-NH_2, DABCO, Yb(OTf)$_3$, 4 Å MS, THF, rt, 24 h; c) CH_2=CH-CN, DABCO, rt, 36 h

Scheme 1 Synthesis of ferrocenyl MBH adducts **2–7**.

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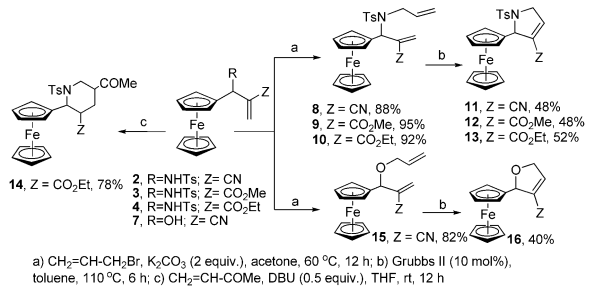


Scheme 2 Synthesis of ferrocenyl N/O heterocycles **11–14** and **16**.

dihydrofuran derivatives, next we focussed on the synthesis of ferrocenyl piperidine derivative **14**. Gratifyingly, [4 + 2]-annulation reaction[12] 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).

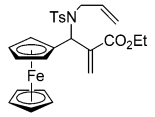
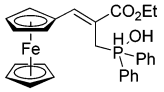
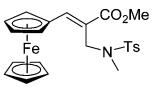
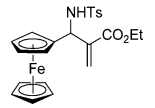
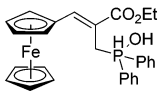
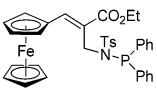
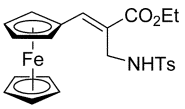
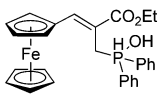
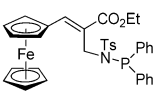
Synthesis of ferrocenyl P/N ligands

Next, keeping the goal of synthesis of structurally varied chiral ligands in mind, we investigated the directive orthometalating 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).

Metallation followed by phosphinylation reaction of unprotected MBH adduct **4**, afforded rearranged *N*-phosphinylated product **21** along with **19** (Table 1, 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 Fc stabilises the rearranged product having NH moiety away from the Fc 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 in very good yield.

Then we turned our attention towards the ferrocenyl heterocycles, where the N/O pendant responsible for planar chiral induction is fixed in the cyclic framework attached to Fc-

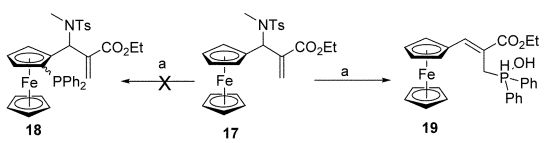
Table 1 Efforts to synthesise acyclic chiral ligands from MBH adducts

Entry	MBH adduct	Product[a] (yield %) A	B
1	 **10**	 **19** (95)	—
2	 **20**	—	—
3	 **4**	 **19**(40)	 **21**(50)
4	 **6**	 **19**(48)	 **21**(47)

[a] (i) TMEDA (1.3 equiv.), *n*-Bu Li (2.5 equiv.), THF, −78 °C, 1 h; (ii) PPh_2Cl (1.3 equiv.), −78 °C–rt, 12 h.

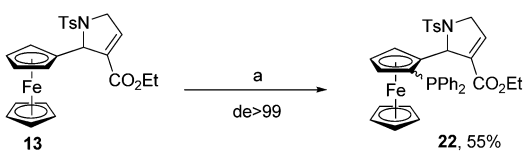
scaffold. The ferrocene matrix bearing pyrrolidine pendant **13** was chosen as the model substrate and its ability to undergo diastereoselective ortholithiation–phosphinylation was first investigated. Thus, treatment of THF solution of **13** at −78 °C with TMEDA and *n*-BuLi followed by quenching with phosphinyl chloride (−78 °C–rt) afforded novel planar and central chiral (racemic) ferrocenyl P,N ligand **22** in moderate yield with excellent diastereoselectivity (de > 99) (Scheme 4).

The structure of chiral ferrocenyl ligand **22** was established by spectroscopic (^{1}H NMR, IR and Mass), multinuclear ($^{13}C\{^1H\}$, $^{31}P\{^1H\}$) and 2DNMR techniques. The ^{1}H 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 $^{13}C\{^1H\}$NMR spectra confirmed the structure by combining the signals of the



a) i). TMEDA (1.3 equiv.), n- BuLi (2.5 equiv.),THF, -78°C, 1 h; ii). PPh_2Cl (1.3 equiv.), -78 °C-rt, 12 h

Scheme 3 Attempted synthesis of acyclic chiral ligand **18**.



a (i). TMEDA (1.3 equiv.), n-BuLi (2.5 equiv.), THF, -78 °C, 1 h; (ii) PPh_2Cl (1.3 equiv.), -78 °C-rt, 12 h

Scheme 4 Synthesis of ferrocenyl P,N ligand **22**.

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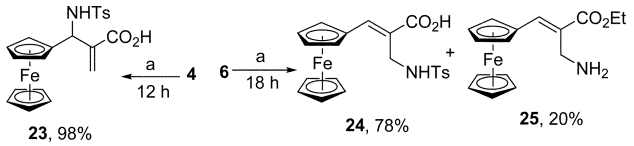
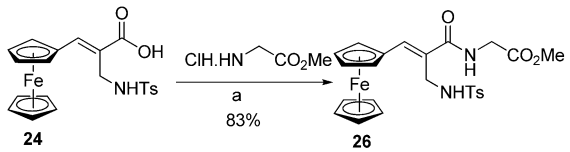


Scheme 5 Synthesis of ferrocenyl amino acids **23** and **24**.

PPh_2 substituted ferrocene unit and pyrrolidine pendant with C═O resonances δ_C 172.4 ppm for ester carbonyl and alkene carbons at δ_C 136.1, 88.4 ppm, respectively. Finally, the $^{31}P\{^1H\}$ NMR spectrum displayed a resonance at δ_P −16.17 ppm.

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.[13] Till now there is no attempt to synthesise stereochemically constrained dehydro-β-amino acid residues incorporating an organometallic scaffold such as ferrocene. 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 **6** under basic condition. During the hydrolysis of rearranged amino ester **6**, along with acid **24** detosylated amine **25** was also obtained in 78% and 20% yields, respectively (Scheme 5).



Scheme 6 Synthesis of ferrocenyl short peptide **26**.

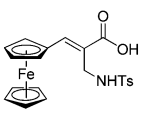
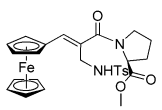
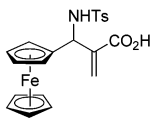
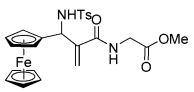
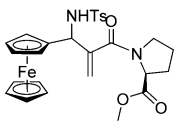
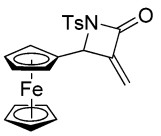
The α-dehydro-β-amino acid **24** was converted into dipeptide **26** with glycine ester hydrochloride by solution phase coupling reaction using EDC as coupling agent (Scheme 6).

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 corresponding short peptide **27** (Table 2, entry 1). Similarly, dehydro ferrocenyl amino acid **23** with glycine and L-proline yielded dipeptides **28** and **29**, respectively (Table 2, entries 2 and 3). The synthetic potential of β-amino acid **23** to yield ferrocenyl β-lactam **30** was demonstrated by reacting **23** in THF with coupling agent bis(2-oxo-3-oxazolidinyl) phosphinic chloride (BOPCl) at room temperature (Table 2, entry 4). Indeed, these simple easy to prepare MBH derived strained ferrocenyl-β-aminoacids can be coupled with PNA's and biogenic peptides like enkephalin and bradykinin analogues for organometallic labelling like Sonogashira and click reaction.[3a,14]

Conclusions

In conclusion, the synthesis of novel multisubstituted ferrocenyl pyrrolidines, furan and piperidine from MBH adducts of

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

Entry	Fc-amino acid	Amino acid	Dipeptide	Yield (%)
1	 **24**	HCl·H-(L)Pro-OMe	 **27**	88[a]
2	 **23**	HCl·H-Gly-OMe	 **28**	84[a]
3	**23**	HCl·H-(L)Pro-OMe	 **29**	86[a]
4	**23**		 **30**	70[b]

[a] Amino acid (1 equiv.), EDC·HCl (3 equiv.), HOBt·H_2O (3.5 equiv.), DIPEA (5 equiv.), DCM : DMF (1 : 1), 0 °C–rt, 12 h. [b] BOPCl (1.5 equiv.), DIPEA (1.5 equiv.), THF, rt, 12 h.

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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.

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