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Activated Alkene Dependent One-Pot, Three-Component Aza-Morita–Baylis–Hillman Reaction of Ferrocenealdehyde: Synthesis of Highly Functionalized Diverse Ferrocene Derivatives

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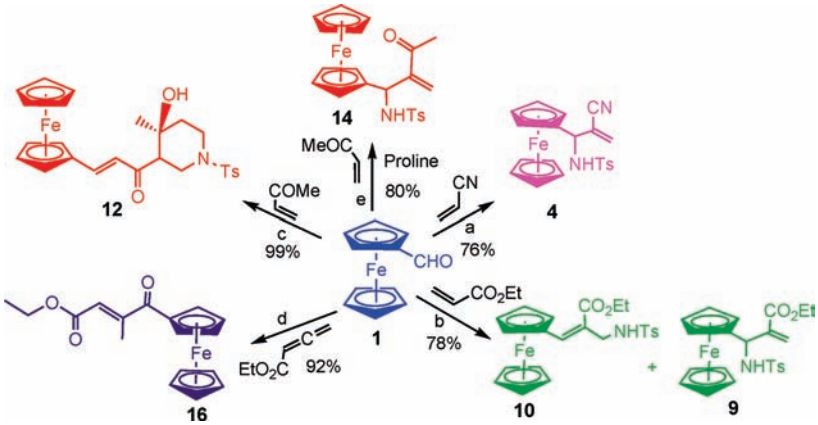
ABSTRACT



Activated alkene dependent one-pot, three-component aza-Morita–Baylis–Hillman (aza-MBH) reaction of ferrocenealdehyde afforded simple aza-MBH adduct of ferrocenealdehyde, unusual piperidine, β-amino acid residue, and γ-ketoester derivatives of ferrocene in good yield. The synthetic protocol with MVK has led to an unexpected ferrocenyl piperidine derivative in an excellent yield via diastereoselective domino aza-Michael/double Aldol pathway. Plausible mechanisms for the formation of unusual products and diastereoselectivity have also been described. The products can be used for the concise synthesis of ferrocenyl nitrogen heterocycles and bioconjugates.

Since the discovery of ferrocene,[1] the fascinating sandwich compound has captured the attention of both organic and inorganic chemists owing to its applications in organic synthesis,[2,3] asymmetric catalysis,[4] development of new materials,[5] and bio-organometallic chemistry.[6] Especially,

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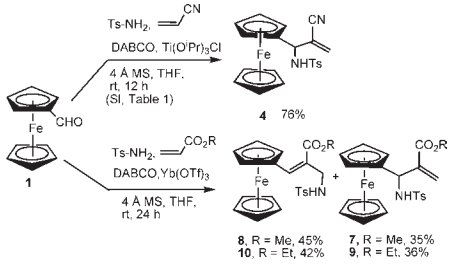
ferrocene appended nitrogen heterocycles play a key role as scaffold for ligands in asymmetric synthesis.[7] In the recent past, bioconjugates of ferrocene have also been studied mainly due to their attractiveness as redox-active biomolecular probes and structural models for peptides.[8] The aza-Morita−Baylis−Hillman (aza-MBH) reaction provides direct access to functionalized chiral amines from achiral substrates and they have been used as synthons for the synthesis of heterocycles and in peptidomimetics.[9] By exploiting the one-pot aza-MBH reaction of ferrocenealdehyde (Fc-CHO) with various amines and Michael acceptors, ferrocene bearing nitrogen functionalities can be synthesized and further manipulated.

The main challenges observed in the one-pot aza-MBH reaction are the chemoselectivity (due to competitive simple MBH reaction) and low yield.[10] To prevent the competitive simple MBH reaction, two-step aza-MBH reaction viz. imine formation followed by reaction with Michael acceptor is widely used and is still being developed. Thus, in the present scenario, a highly chemoselective, one-pot, aza-MBH reaction with good yields at room temperature is warranted. Our interest in MBH reaction[11] led us to the first highly chemoselective, one-pot, three-component synthesis of aza-MBH adducts of Fc-CHO, which provided highly functionalized diverse ferrocene derivatives. Recently, we have reported the synthesis of one- and two-arm functionalized ferrocene derivatives by using a simple MBH reaction that had been further used in the preparation of novel materials and macrocycles.[12]

Initially, we have carried out a reaction of Fc-CHO **1** in 2-propanol, with tosyl amine ($TsNH_2$) **2**, acrylonitrile **3**, 50 mol % of DABCO as catalyst, and 4 Å MS as additive at rt for 12 h. The reaction afforded aza-MBH adduct, namely, β-amino-α-methylene nitrile **4** in 52% yield (Scheme 1). To optimize the reaction, a number of experiments were carried out by varying catalysts (bases and Lewis acids) and solvents (see SI, Table 1). An ideal condition was found to be 50 mol % of DABCO and 2 mol % of $Ti(O^iPr)_3Cl$ in THF to yield 76% of adduct **4** (SI, Table 1, entry 6). It is noteworthy that even a trace of the simple MBH product was not detected, thanks to the inherent low reactivity of Fc-CHO as an electrophile compared to ferrocenyl imine.

The successful use of acrylonitrile prompted us to use methyl acrylate as a Michael acceptor, which would directly provide α-substituted β-amino ferrocenyl ester. Due to the continuous growth of pharmaceutical and biological importance of β-amino acids[13] and scant reports known for the synthesis of its ferrocenyl derivatives,[14] a simple and efficient synthetic method is highly appreciable. Thus, the reaction of Fc-CHO with methyl acrylate **5**, $TsNH_2$, and DABCO afforded aza-MBH adduct **7** and its isomerized derivative **8** in 35% and 45% yields, respectively (Scheme 1). It should be noted that the isomerized adduct **8** was formed in a one-pot manner that usually needs a subsequent isomerization step or an additional reagent.[12] To the best of our knowledge this is the first report on the synthesis of ferrocenyl-β-amino acid derivatives by aza-MBH reaction thus making an introduction into bio-organometallic chemistry.

Scheme 1. Synthesis of Aza-MBH Adducts **4**, **7**, and Isomerised Derivative **8**



Methyl vinyl ketone **11** (MVK) as a Michael acceptor is widely known for its high reactivity to form unusual MBH products,[9,15] which prompted us to use it in the aza-MBH reaction of Fc-CHO.[16] Thus, Fc-CHO with MVK in the presence of DABCO under optimized condition provided an unexpected ferrocenyl piperidine derivative **12a** in 15% yield as a single diastereomer (Scheme 2). To improve the

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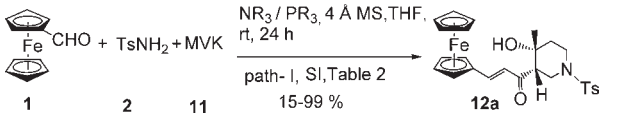
(16) Also it is to be noted that during our investigation in MBH adduct formation, we found both ferrocene mono and bis aldehydes were reluctant to form corresponding adducts with Michael acceptors like acrylates, methyl vinyl ketone, phenyl vinyl sulfones, amides, cyclic enones, allenes, etc.

yield of **12a**, a number of bases were screened and tris(2,6-dimethoxyphenyl)phosphine was found to be the best catalyst to yield **12a** in 99% with traces of the other diastereomer (dr 99:1) (SI, Table 2, entry 6). During the investigation we observed that stronger bases like DBU and PBu_3 provided **12a** in better yields than DABCO and PPh_3[17](SI, Table 2).

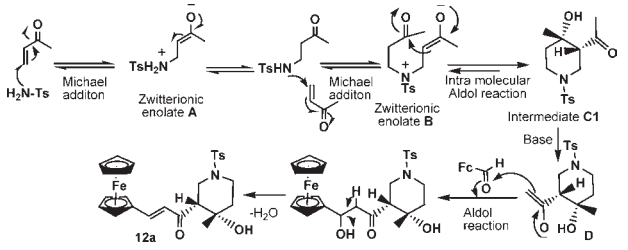
Scheme 2. Synthesis of Ferrocenyl Piperidine Derivative **12a**



The structure of compound **12a** was established by spectroscopic data and confirmed by single crystal X-ray analysis of **13**,[18] which has been derived from **12a**. (SI, Scheme 1, Figure 1).

A mechanistic proposal for the formation of the unprecedented piperidine derivative **12a** is outlined in Scheme 3. The mechanism can be best explained by invoking a diastereoselective domino aza-Michael/double Aldol reaction pathway. At first, MVK undergoes Michael addition with Ts-NH_2 instead of DABCO to give the zwitterionic enolate **A**, which again adds to another molecule of MVK to form zwitterionic enolate **B**.[10c] The enolate **B** undergoes an intramolecular Aldol reaction to afford six-membered intermediate **C**,[19] which on another Aldol condensation with Fc-CHO gave the ferrocenyl piperidine derivative **12a** (dr 99:1). To date, no reports are available for such type of highly diastereoselective domino aza-Michael/double Aldol reaction.

Scheme 3. Proposed Mechanism for the Formation of Compound **12**



However, we reasoned that isolation of the six-membered intermediate **C** would be important to support the proposed mechanism. Interestingly when we carried out a blank experiment without Fc-CHO under the optimized condition, intermediates **C1** and **C2** have been isolated as diastereomers in 3:2 ratio (Figure 1). The reaction of Fc-CHO with a mixture of **C1** and **C2** in the presence of DBU furnished product **12a** with another diastereomer **12b** (dr 3:2). To explain the role of Fc-moiety in controlling the diastereoselectivity observed in the one-pot reaction, a number of experiments were carried out with various alkyl, aryl aldehydes and ketone instead of Fc-CHO and none of them provided the final piperidine derivative. The observed diastereoselectivity in ferrocenyl piperidine formation can be rationalized by means of conformational analysis of diastereomers **12a** and **12b** (Figure 1). The predominance of diastereomer **12a** over **12b** may be due to the more favorable conformation achieved by the equatorial orientation of anchoring ferrocenyl moiety, intramolecular hydrogen bonding between hydroxyl group and ketone, and the absence of two gauche butane interactions. Thus, we hypothesize that during the course of the reaction formation of thermodynamically more stable isomer **12a** directs the intermediate equilibrium toward **C1** from **C2**, which results in the selective formation of piperidine derivative **12a** rather than **12b** (dr 99:1).

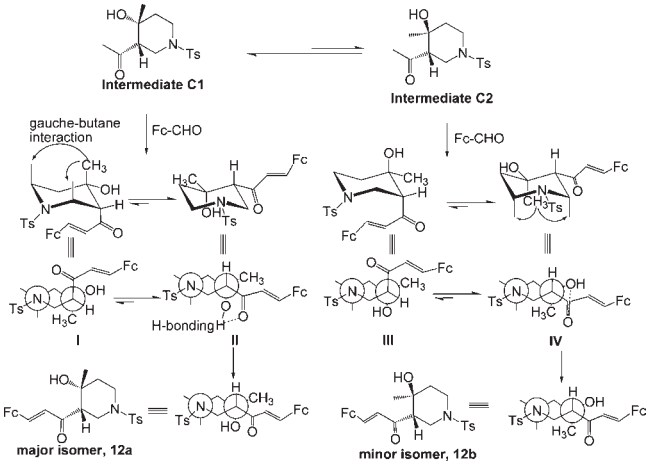


Figure 1. Mechanistic scenario for the formation of diastereoselective ferrocenyl piperidine derivative **12a**.

Proline as a catalyst with nucleophilic amine/phosphine bases as cocatalyst is known to activate Michael acceptor in the MBH reaction.[20] Having realized that the formation of unusual product **12** is indeed general and the role of catalyst is quite different as described in the mechanism, we introduced proline in the reaction, which in principle is expected to alter the reaction pathway. Interestingly, the reaction of Fc-CHO with proline (40 mol %) and DABCO as cocatalyst (20 mol %) under optimized condition proceeded smoothly

(17) Low yields for unusual MBH derivatives were reported with weak bases like PPh_3 and DABCO, see: Shi, M.; Xu, Y.-L. *Eur. J. Org. Chem.* **2002**, 696.

(18) The crystallographic coordinates have been deposited with the Cambridge Crystallographic Data Centre; deposition no. 788036. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, UK or via www.ccdc.cam.ac.uk/conts/retrieving.html.

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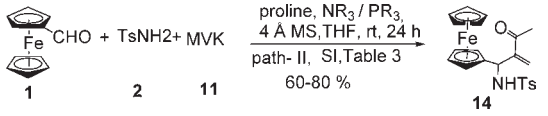
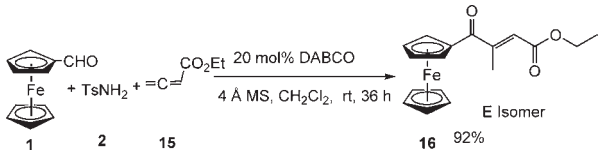
to form the usual aza-MBH adduct **14** in 80% yield (Scheme 4). Screening of a number of cocatalysts did not alter the reaction sequence or improve the yield (see SI, Table 3). In the dual-catalyzed aza-MBH reaction, proline and base together accelerate the formation of eneamine, which subsequently reacts with Fc-imine to give adduct **14**. The Michael addition of Ts-NH_2 to MVK and formation of iminium ion with proline are the two competing reactions where the later succeeds to form the usual aza-MBH adduct. Herein, by a judicious selection of catalysts combination, it is possible to switch over to two different catalytic pathways I or II, which lead to two different products (**12** or **14**).

Scheme 4. Synthesis of Aza-MBH Adduct **14**



The interesting activated alkene dependent reactivity profile shown by Fc-CHO in aza-MBH reactions described above prompted us to test the reactivity of activated allenes in this series. The reaction of Fc-CHO with $TsNH_2$ and ethyl-2,3-dienoate **15** in the presence of DABCO under optimized condition did not give any product. However, with 2 equiv of **15** after 36 h, an unusual γ-keto ester derivative of ferrocene **16** was obtained in 92% (recovered yield) (Scheme 5). Lewis bases like DMAP and P(tolyl)$_3$ did not improve the yield. Reaction with substituted allenoate viz. ethyl penta-2,3-dienoate gave only Fc-imine.

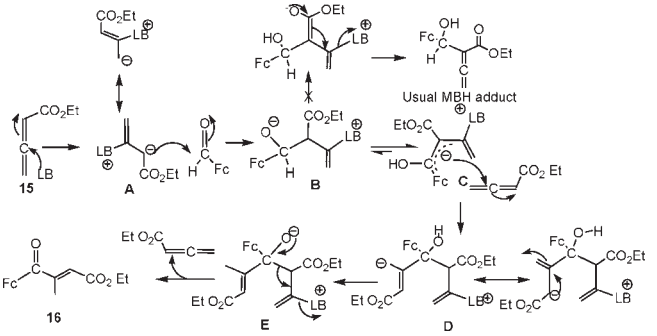
Scheme 5. Synthesis of the γ-Ketoester of Ferrocene **16**



The formation of **16** can be rationalized by a plausible mechanistic pathway (Scheme 6). The enolate **A** generated by the Michael addition of Lewis base to allene adds to Fc-CHO to form intermediate **B**, which is in equilibrium with more stable intermediate **C**. The formation of intermediate **C** may be facilitated by ferrocene and allene moiety resulting in the polarity reversal at the Fc-carbonyl center. Nucleophilic addition of **C** with another molecule of allene followed by proton transfer and elimination of one molecule of allene resulted in the formation of unexpected γ-ketoester derivative **16**. It is to be noted that, in the absence of Ts-NH_2 and DABCO, no reaction has occurred, but its exact role is not clear at the current stage of development.

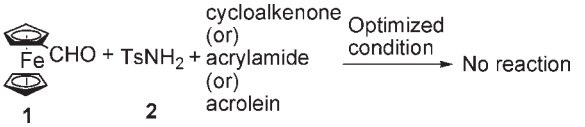
It should also be noted that the two-pot reaction viz. Pre formed Fc-imines with Michael acceptors used above failed to provide the expected aza-MBH adducts or unusual derivatives.

Scheme 6. Plausible Mechanism for the Formation of the γ-Ketoester Derivative of Ferrocene **16**



To our dismay, the aza-MBH reaction of Fc-CHO with Michael acceptors such as acryl amide, cyclohexenone, cyclopentenone, and acrolein under optimized and altered conditions were unsuccessful (Scheme 7).

Scheme 7. Attempted aza-MBH reactions with Fc-CHO



In conclusion, we have demonstrated the first one-pot, three-component and Michael acceptor dependent aza-MBH reaction of Fc-CHO, which offered a number of novel and diverse ferrocene derivatives. Unexpected Fc-piperidine derivative was obtained with excellent diastereoselectivity by an unprecedented domino Michael/double Aldol condensation pathway. The unusual products observed in the reaction of Fc-CHO with MVK and allene as Michael acceptors have never been disclosed before, which is important from both synthetic and mechanistic points of view. Efforts aimed at developing asymmetric ferrocenyl ligands, redox-active cyclic peptides, and peptide foldamers by using the reported products are currently underway in our laboratory.

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Supporting Information Available. Detailed experimental procedure, optimization data tables, characterization of the products, and copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.