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A facile one-pot three-component synthesis of ferrocene-grafted dispiro pyrrolidine/pyrrolizidine scaffolds through intermolecular [3+2] cycloaddition reaction of ferrocenyl Baylis–Hillman adduct

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ABSTRACT

A one-pot synthesis of ferrocene-grafted dispiropyrrolidine/pyrrolizidine scaffolds has been accomplished in good yields through a facile 1,3-dipolar cycloaddition of various azomethine ylides derived from diketones and secondary amino acids with Baylis–Hillman adduct derived from ferrocene carbaldehyde. The regiochemical and stereochemical outcomes of the cycloaddition reaction were ascertained by X-ray crystallographic studies of one of the cycloadducts.

Multicomponent reactions[1] (MCRs) constitute an attractive synthetic strategy in synthetic methodology, allowing the construction of complex molecular architectures, from easily available starting materials in a single synthetic operation without the need for isolation of intermediates.

Ferrocene derivatives containing heterocyclic systems have attracted special attention in recent years,[2–7] because of their organic and inorganic properties as well as for their applications in various areas of organic materials.[8–11] Ferrocene is now currently employed in signaling probes for the detection of estrogen receptors,[12] dinucleotides,[13] and DNA hybridization,[14] thus opening the way to gene sensors[15] and has found extensive application in drugs.[16–18] In the light of current studies, the combination of ferrocene units with heterocyclic molecules offers a way to endow novel functional molecules.[19–21]

The pyrrolidine moiety is one of the significant core structures among the most extensively studied natural and unnatural heterocyclic compounds with remarkable medicinal activities.[22] In particular, pyrrolidine and its fused derivatives such as pyrrolizidines and indolizidines have played a unique role in the design and synthesis of novel biologically active compounds, serving as anti tuberculosis, anti bacterial, anti hypertensive, anti tumor, and most notably anti malarial agents.[23] Consequently integration of a ferrocene moiety with pyrrolidine derivatives may increase their biological activities or create new medicinal properties.

In recent years, the Baylis–Hillman reaction has become a powerful and useful synthetic tool for the atom economical construction of a C–C bond, which has wide applications in various organic transformations and is well documented in the literature.[24] Recently there has been a report wherein ferrocenylphosphine was used as a catalyst for B–H reaction.[25] Here we utilize the B–H adduct prepared from ferrocenyl aldehyde as a dipolarophile for the synthesis of novel ferrocene-grafted heterocycles. The intermolecular 1,3-dipolar cycloaddition reaction is one of the efficient methods for the construction of heterocyclic units in a highly regioselective and stereoselective manner.[26] In particular, the chemistry of azomethine ylides has gained significance in recent years as it serves as an expedient route for the construction of nitrogen containing five-membered heterocycles, which constitute the central skeleton of numerous natural products.[27,28] In continuation of our research interest in the area of 1,3-dipolar cycloadditions,[29] we herein report for the first time a simple one-pot three-component protocol for a facile transformation of the ferrocenyl Baylis–Hillman adducts into mono/bicyclic heterocyclic frameworks containing a pyrrolidine/pyrrolizidine moiety through the reaction of the azomethine ylide generated from diketones and various secondary aminoacids with ferrocene-based Baylis–Hillman adduct **3**.

Methyl-2-(2,3-dihydro-2-hydroxy-1*H*-ferrocene-2-yl) acrylate **3**, which was synthesized by the Baylis–Hillman reaction of ferro-

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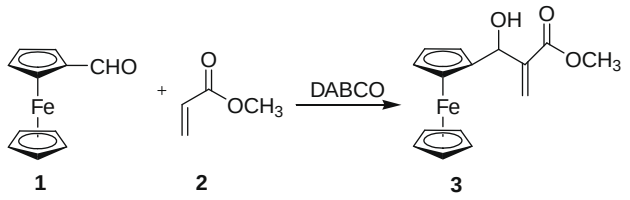
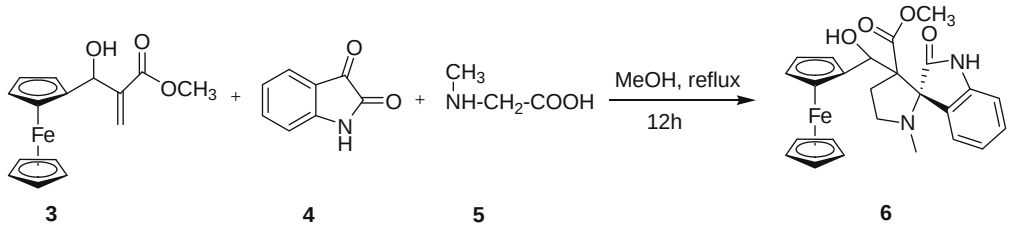


Scheme 1. Synthesis of ferrocenyl Baylis–Hillman adduct.

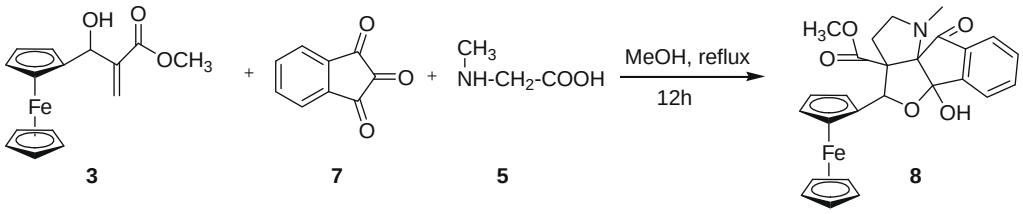
cenecarbaldehyde **1** and methyl acrylate **2** in the presence of 0.1 equiv of DABCO as a catalyst (Scheme 1), was utilized as a dipolarophile for the first time. Schemes 2–4 depict the one-pot, three-component reactions involving isatin **4**, ninhydrin **7**, acenaphthaquinone **9**, sarcosine **5**, proline **11**, and ferrocenyl Baylis–Hillman adduct **3** for the synthesis of novel ferrocenyl dispiropyrrolidines and pyrrolizidines **6**,**8**,**10**,**11**,**13–16**.

The Baylis–Hillman adduct **3** underwent smooth reaction with non-stabilized azomethine ylide generated from isatin **4** and sarcosine **5** in refluxing methanol, affording the ferrocenyl dispiropyrrolidine **6** in good yield (Scheme 2, Table 1, entry 1). The formation of the cycloadduct **6** was confirmed by spectral and elemental analyses. In the ^{1}H NMR spectrum of **6,** the –NCH_3 proton exhibited a singlet at δ 1.96. The –NCH_2 protons of the pyrrolidine ring appeared as multiplets in the region δ 2.43–2.58. The ferrocenyl protons exhibited singlets at δ 4.06 and δ 4.13. The aromatic protons exhibited multiplets in the region δ 6.91–7.19. The off-resonance proton decoupled ^{13}C NMR spectra of **6** exhibited peaks for the –NCH_3 carbon and spirocarbons at δ 35.41, δ 71.77, and δ 77.30. The oxindole carbonyl group appeared at δ 176.94. Furthermore, the regiochemical and stereochemical outcomes of the cycloaddition reaction were unambiguously ascertained by single-crystal X-ray analysis of the cycloadduct **6** (Fig. 1).[30] As outlined in Table 1, a number of ferrocene-substituted cycloadducts were synthesized in good to excellent yields. The structures and the stereochemistry of the cycloadducts were confirmed by spectral analysis.[31,32]

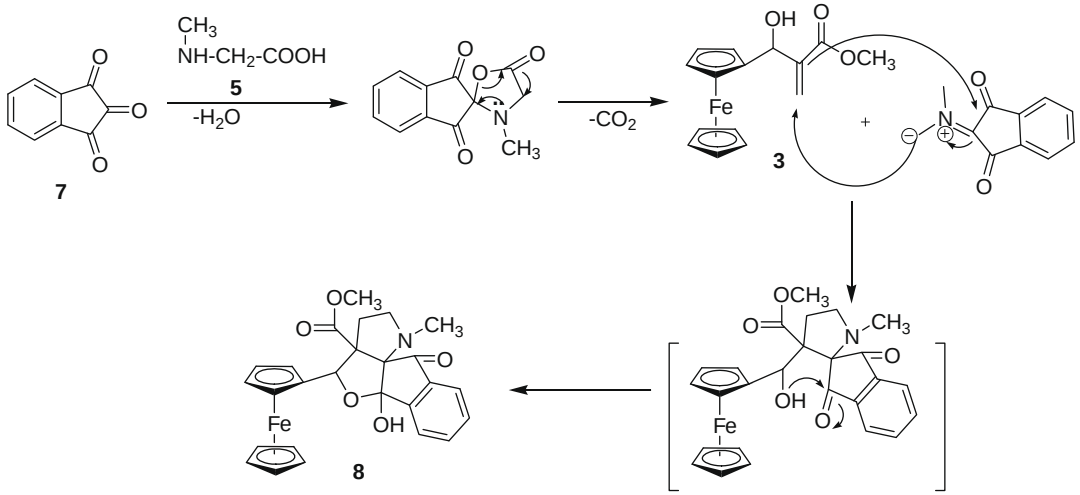
In another experiment, the reaction of azomethine ylide generated from ninhydrin **7** and sarcosine **5** with Baylis–Hillman adduct **3** in refluxing methanol yielded the cycloadduct **8** in good yield (Scheme 3, Table 1, entry 2). In this experiment the cycloadduct



Scheme 2. Synthesis of ferrocenyl dispiropyrrolidine.

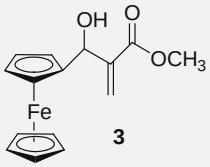
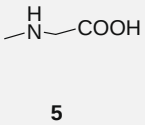
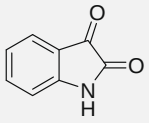
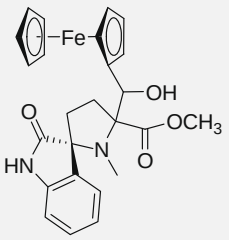
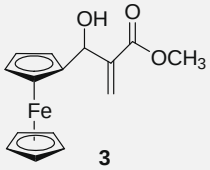
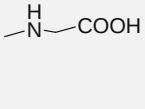
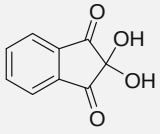
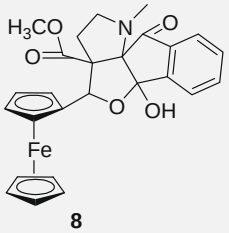
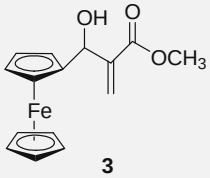
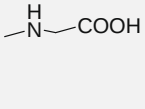
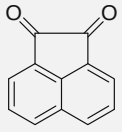
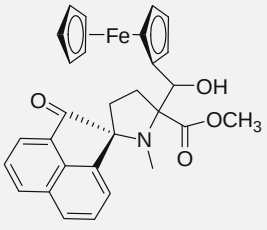
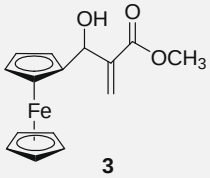
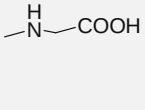
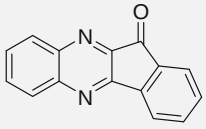
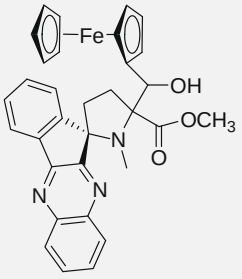


Scheme 3. Synthesis of ferrocenyl pyranopyrrolidine.



Scheme 4. Mechanism for the synthesis of pyranopyrrolidine.

Table 1
Three component synthesis of ferrocenyl dispiropyrrolidine/pyranopyrrolidine scaffolds involving intermolecular [3+2]-cycloaddition.

Entry	Components			Products[a]	Time (h)	Yield[b] (%)
	A	B	C			
1	 **3**	 **5**	 **4**	 **6**	12	83
2	 **3**	 **5**	 **7**	 **8**	12	80
3	 **3**	 **5**	 **9**	 **10**	14	63
4	 **3**	 **5**	 **12**	 **11**	12	71

[a] Isolated products were characterized by ^{1}H NMR, ^{13}C NMR, mass, and X-ray diffraction analysis.
[b] Yields refers to pure isolated products after purification by silica gel column chromatography.

initially formed underwent intramolecular cyclization because of the proximity of the carbonyl group to give furanopyrrolidine **8** (Scheme 4). The structure of the compound was established by single crystal X-ray diffraction analysis (Fig. 2).[32]

The three-component reaction was applied to the preparation of the ferrocene-based spiropyrrolizidines **13–16** by reacting ferrocenyl Baylis–Hillman adduct **3**, proline **11**, and diketones **4**, **7**, **9**, and **12** (Table 2, entries 1–4). In all cases the cycloaddition reaction was extremely fast and could be conducted in one-pot. The scope of the reaction sequence allows the preparation of diversely functionalized pyrrolizidine rings fused to a ferrocene. As expected, the regiochemical and stereochemical outcomes of the products were confirmed by spectral and elemental analyses.

In summary, we have demonstrated that the MCR could be used for synthesizing novel ferrocene-grafted dispiro pyrrolidine and pyrrolizidine scaffolds through one-pot three-component intermolecular [3+2] cycloaddition of azomethine ylides with unusual ferrocene-derived Baylis–Hillman adduct. A wide range of pyrrolidine scaffolds can be prepared having a substitution pattern controlled by the selection of the reactants. At present no multicomponent reaction leading to pyrrolidine derivatives having ferrocene functionality derived from Baylis–Hillman adduct of ferrocene carbaldehyde derivatives offers such a high level of functional, structural, and stereochemical diversity. We are optimistic that this highly flexible and robust methodology will provide quick and easy access to complex molecular structures, which are of therapeutic interest.

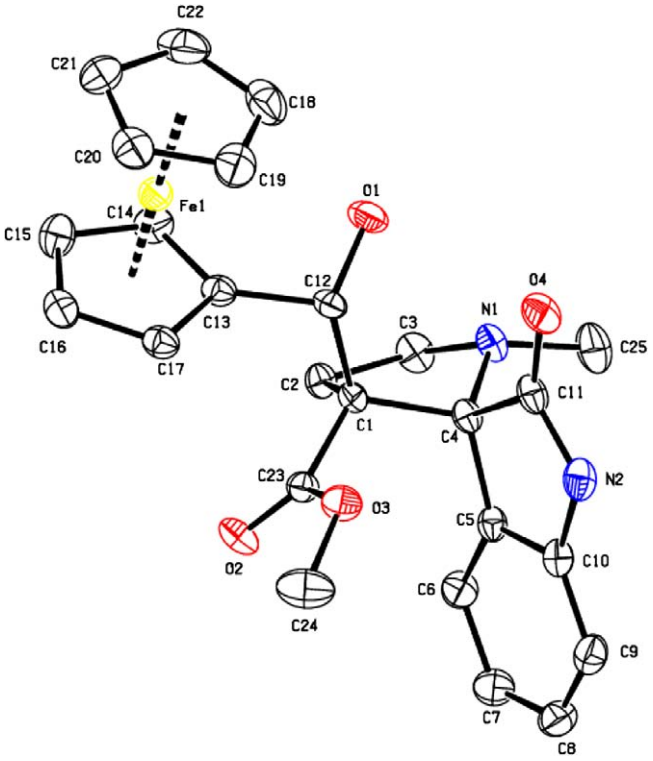


Figure 1. ORTEP diagram of compound **6**.

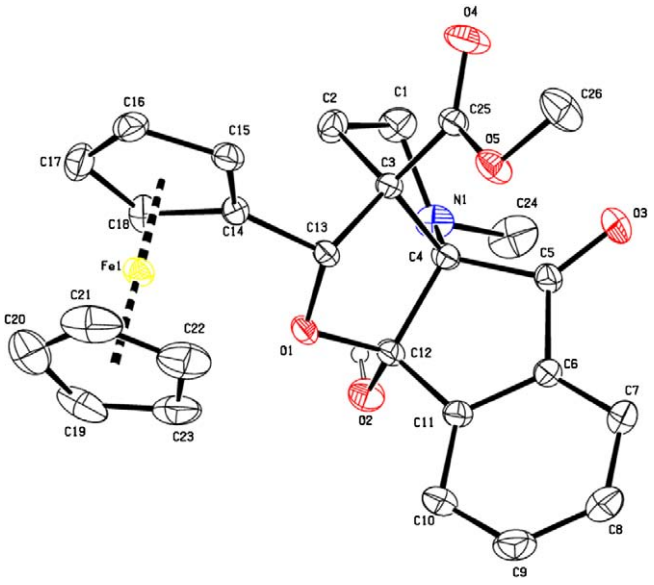
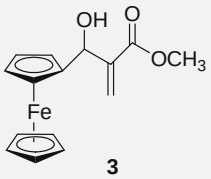
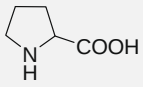
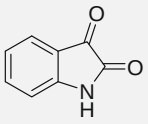
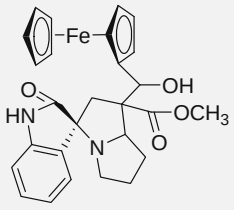
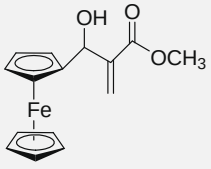
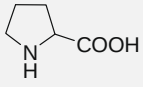
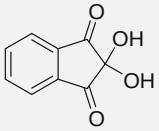
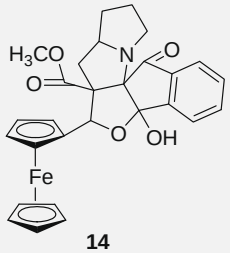
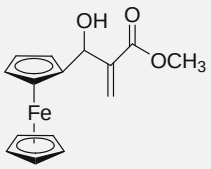
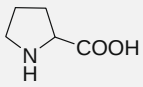
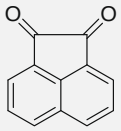
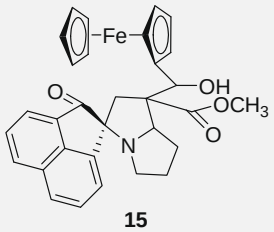


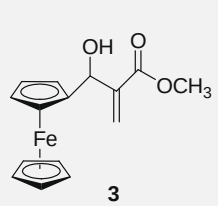
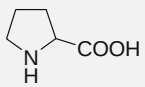
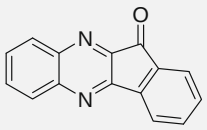
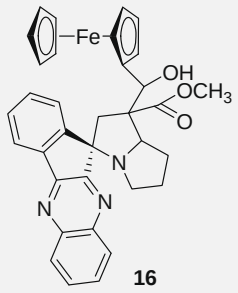
Figure 2. ORTEP diagram of compound **8**.

Table 2
Three component synthesis of ferrocenyl dispiropyrrozidine/pyranopyrrolizidine scaffolds involving intermolecular [3+2]-cycloaddition.

Entry	Components			Products[a]	Time (h)	Yield[b] (%)
	A	B	C			
1	 **3**	 **11**	 **4**	 **13**	13	72
2	 **3**	 **11**	 **7**	 **14**	11	77
3	 **3**	 **11**	 **9**	 **15**	13	72

(*continued on next page*)

Table 2 (*continued*)

Entry	Components			Products[a]	Time (h)	Yield[b] (%)
	A	B	C			
4	 **3**	 **5**	 **12**	 **16**	12	70

[a] Isolated products were characterized by ^{1}H NMR, ^{13}C NMR, mass, and spectral analysis.
[b] Yields refers to pure isolated products after purification by silica gel column chromatography.

Acknowledgments

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31. *Representative experimental procedure for the synthesis of ferrocenyl Baylis–Hillman adduct* **3**: A mixture of ferrocenecarboxaldehyde (0.5 g, 2.3 mmol), methylacrylate (0.12 g, 2.3 mmol), and 1,4-diazabicyclo[2.2.2]octane (DABCO, 0.05 g, 0.4 mmol) was allowed to stand at rt for two days. The product mixture was dissolved in Et_2O (100 ml), washed with 10% dil HCl (50 ml) and then with water (50 ml) and dried (Na_2SO_4). The solvent was removed to obtain a solid, which was purified by column chromatography (silica gel, hexane/EtOAc, 99:1), to obtain a yellow solid.
Ferrocene Baylis–Hillman adduct **3**: R_f −0.1, (hexane/ethylacetate, 99:1) yellow solid, yield 62%. mp 78 °C. ^{1}H NMR (300 MHz, $CDCl_3$); δ 3.75 (s, 3H); 4.22 (s, 9H); 5.27 (s, 1H); 5.84 (s, 1H); 6.21 (s, 1H); ^{13}C NMR (75 MHz $CDCl_3$); δ 51.86, 65.89, 67.97, 68.58, 68.75, 69.69, 70.30, 70.66, 91.77, 124.95, 142.18, 166.83; *m/z* 298.7 (M^+). Elemental Anal. Calcd for $C_{15}H_{15}O_3Fe$: C, 60.20; H, 5.01. Found: C, 60.34; H, 5.11.
Representative procedure for the synthesis of ferrocene grafted dispiropyrrolidine/pyrrolizidine derivatives **6**,**7**,**10**,**11**: A mixture of ferroceneyl Baylis–Hillman adduct (1.0 equiv), secondary amino acid sarcosine/proline (1.2 equiv) and the corresponding diketone (1.2 equiv) was heated under reflux in methanol. After completion of the reaction as evidenced by TLC, the solvent was removed under reduced pressure. The crude product was subjected to column chromatography using silica gel with petroleum ether/ethyl acetate (3:2) as eluent to get pure product.
Dispiropyrrolidine **6**: R_f −0.6, (hexane/ethylacetate, 3:1) yellow solid, yield 82%. mp 176–178 °C. ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.96 (s, 3H); 2.43–2.58 (m, 2H); 2.81–2.88 (m, 1H); 3.01 (s, 3H); 3.30 (m, 1H); 3.72 (s, 1H); 3.90- 4.06 (m, 3H); 4.15 (s, 5H); 4.41 (s, 1H); 5.31 (s, 1H); 6.86–7.19 (m, 4H); 8.73 (s, 1H); ^{13}C NMR (75 MHz $CDCl_3$); δ 24.56, 35.41, 50.92, 51.32, 52.41, 65.77, 66.80, 67.10, 67.73, 67.90, 68.87, 71.77, 77.30, 87.57, 110.01, 122.47, 125.93, 129.41, 138.68, 140.55, 170.93, 176.94; *m/z* 472.9 (M^+). Elemental Anal. Calcd for $C_{25}H_{26}N_2O_4Fe$: C, 63.42; H, 5.28; N, 5.91. Found: C, 63.53; H, 5.40; N, 5.83.
Dispiropyrrolidine **8**: R_f −0.5, (hexane/ethylacetate, 3:2) yellow solid, yield 83%; ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.81–1.98 (m, 2H); 2.46 (s, 3H); 3.26 (d, J = 2.1 Hz, 1H); 3.29 (d, J = 2.7 Hz, 1H); 3.66 (s, 3H); 3.75 (s, 1H); 4.00 (s, 1H); 4.10 (s, 5H); 4.12 (s, 1H); 4.16 (d, J = 1.2 Hz, 1H); 4.42 (s, 1H); 4.65 (s, 1H); 7.59–8.03 (m, 4H); ^{13}C NMR (75 MHz $CDCl_3$); δ 29.03, 37.93, 52.44, 57.91, 66.14, 66.59, 67.75, 68.02, 68.56, 69.02, 70.08, 82.23, 86.08, 102.30, 122.87, 124.99, 130.62, 136.93, 137.17, 150.18, 171.53, 199.14; *m/z* 486.9 (M^+). Elemental Anal. Calcd for $C_{26}H_{25}NO_5Fe$: C, 64.06; H, 5.13; N, 2.87. Found: C, 64.20; H, 5.24; N, 3.00.
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