



An efficient copper catalyzed one-pot, four-component, and diastereoselective synthesis of highly functionalized ferrocenyl azetidines

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ABSTRACT

An efficient, facile, and diastereoselective synthesis of highly functionalized ferrocenyl azetidines from copper catalyzed one-pot, four-component reaction of ferrocenealdehyde, aromatic amines, tosyl azide, and aryl alkynes in high yield has been accomplished. A plausible reaction mechanism is provided.

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Ferrocene¹ molecule has drawn the attention of chemists owing to its applications in organic synthesis,^{2,3} development of new materials,⁴ bio-organometallic chemistry,⁵ and asymmetric catalysis.⁶ Nitrogen heterocyclic compounds of ferrocene are in the current scenario, especially in asymmetric synthesis⁷ and in the development of novel therapeutics⁸ (Fig. 1). Azetidines⁹ and azetidinones¹⁰ are important class of small ring nitrogen heterocyclic compounds found in many natural products and exhibit interesting biological and pharmacological properties.¹¹ Azetidines have been successfully utilized as ligands,¹² catalysts in various asymmetric syntheses¹³ and in ring opening reactions to prepare nitrogen-containing organic compounds.¹⁴ Multicomponent reactions^{15,16} (MCRs) are considered as a powerful tool to generate complex molecular architectures from simple and readily available substrates in a one-pot manner. In recent years, the transition-metal-catalyzed MCRs are of high importance because they have excellent catalytic efficiency in most cases. Nevertheless, it requires harsh conditions; meanwhile, protocols that allow much milder conditions have been developed. Copper (I) catalyzed¹⁷ MCRs concerning sulfonyl azides and alkynes have been extensively used.¹⁸ Fokin et al and Xu et al described a Cu-catalyzed, three-component cascade reaction to generate an impressive array of *N*-sulfonylazetidines^{18a} and 2-(sulfonylimino)-4-(alkylimino) azetidine derivatives,¹⁹ respectively. However, no reports are available in the literature on the

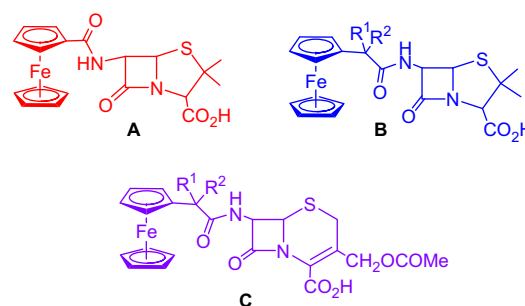
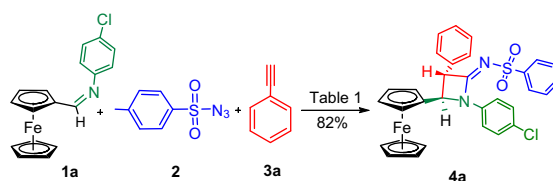


Figure 1. Structure of ferrocenyl–penicillin A and ferrocenyl–penicillin B, and a ferrocenyl–cephalosporin C.



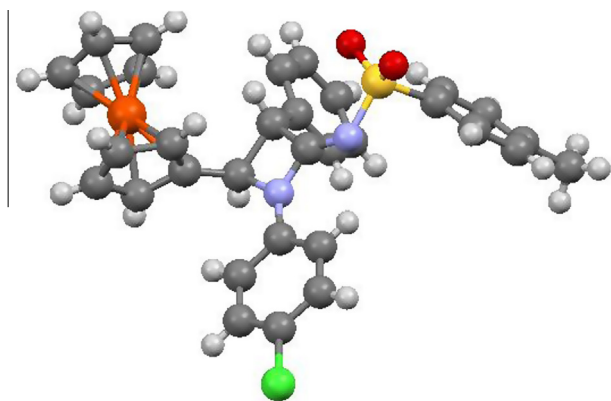
Scheme 1. Synthesis of ferrocenyl azetidininime 4a.

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Table 1
Optimization of synthesis of **4a**

Entry	CuI (mol %)	Solvent	Base (equiv)	Time (h)	% Yield of 4a ^{a,b}
1	20	CH ₃ CN	Et ₃ N (2)	13	75
2	20	CH ₃ CN	Py	14	65
3	20	CH ₃ CN	DABCO	14	45
4	20	CH ₃ CN	K ₂ CO ₃	14	0
5	20	CH ₃ CN	Et ₃ N (1.5)	13	80
6	15	CH ₃ CN	Et ₃ N (1.5)	13	82
7 ^c	10	CH ₃ CN	Et ₃ N (1.5)	13	82
8	10	DCM	Et ₃ N (1.5)	14	60
9	10	THF	Et ₃ N (1.5)	14	43
10	10	Toluene	Et ₃ N (1.5)	14	72
11	10	CH ₃ CN	Et ₃ N (1)	13	65
12	5	CH ₃ CN	Et ₃ N (1.5)	15	50

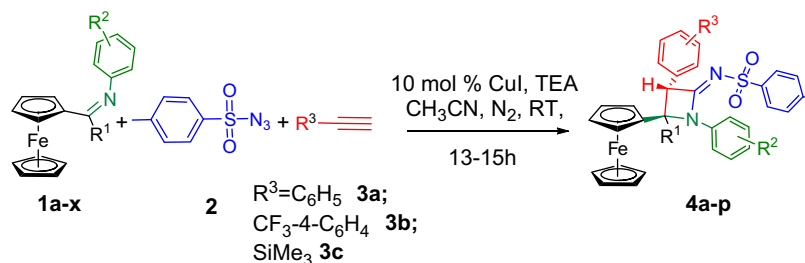
^a All the reactions were performed at room temperature.^b Isolated yield after column purification.^c Optimized condition.**Figure 2.** ORTEP diagram of ferrocenyl azetidiniimine **4a**.

synthesis of ferrocenyl azetidiniimines. Therefore, in continuation of our work on the challenge existed for ferrocene derivatives,²⁰ herein we report an efficient synthesis of ferrocenyl azetidine-2-imines via copper catalyzed alkyne–azide cascade reaction as a key step.

Initially, we investigated a cascade reaction of an equimolar mixture of ferrocenylimine **1a**, *p*-toluenesulfonyl azide **2**, phenyl acetylene **3a**, and activated 5 Å molecular sieves in acetonitrile stirred with 20 mol % CuI and 2.0 equiv of Et₃N under nitrogen atmosphere at room temperature (Scheme 1). The imine **1a** was prepared from ferrocenealdehyde and 4-chloroaniline in toluene at reflux temperature. Thin layer chromatography (TLC) analysis showed the progress of the cascade four-component reaction occurred in 13 h. The reaction afforded a single product of ferrocenyl azetidiniimine **4a** in 75% yield after purification by column chromatography (Table 1, entry 1).

The structure of the compound **4a** was assigned based on spectroscopic analysis such as Fourier transform infrared (FTIR), ¹H nuclear magnetic resonance (NMR), ¹³C NMR, and high resolution mass spectrometry (HRMS). The relative stereochemistry of compound **4a** was derived from single crystal X-ray analysis (Fig. 2).²¹

To optimize the reaction conditions, variables such as base, mol % of Cu catalyst and solvent have been considered. Among the screened bases such as Et₃N, pyridine, DABCO, and K₂CO₃, Et₃N proved to be the most effective for this transformation and provided compound **4a** in 75% yield (Table 1, entries 1–4). Further reducing equivalent of base to 1.5 afforded a marginally improved yield (Table 1, entry 5), while with 1 equiv provided lesser yield (Table 1, entry 11). Loading of CuI was reduced from 20 mol % to 15 mol % and to 10 mol % which had no adverse effect on the product yield (Table 1, entries 5–7). Further decrease in catalyst load (5 mol %) had an inferior product yield (Table 1, entry 12). The reaction in solvents such as CH₂Cl₂, CHCl₃, THF and toluene was surveyed and found to provide lesser yield (Table 1, entries 8–10). An optimum yield was obtained when the reaction was carried out in CH₃CN with 10% of CuI and 1.5 equiv of Et₃N at ambient temperature (Table 1, entry 7).

Table 2
Synthesis of ferrocenyl azetidiniimines **4a–p**

Entry	Imine			Alkyne 3	Azetidine imine 4	% Yield ^a	dr ^c
	R ¹	R ²	1				
1	H	4-Cl-C ₆ H ₄	1a	3a	4a	82	91:9
2	H	4-Me-C ₆ H ₄	1b	3a	4b	84	92:8
3	H	4-OMe-C ₆ H ₄	1c	3a	4c	83	91:9
4	H	4-NMe ₂ -C ₆ H ₄	1d	3a	4d	86 ^b	97:3
5	H	C ₆ H ₅	1e	3a	4e	82	95:5
6	H	4-Br-C ₆ H ₄	1f	3a	4f	79	95:5
7	H	4-F-C ₆ H ₄	1g	3a	4g	73	94:6
8	H	4F-3Cl-C ₆ H ₃	1h	3a	4h	69	97:3
9	H	3-Br-C ₆ H ₄	1i	3a	4i	72	94:6
10	H	3-F-C ₆ H ₄	1j	3a	4j	60	97:3
11	H	4-CF ₃ -C ₆ H ₄	1k	3a	4k	73	95:5
12	H	Naphthyl	1l	3a	4l	81	96:4
13	H	4-Me-C ₆ H ₄	1b	3b	4m	73	94:6
14	H	2-Br-C ₆ H ₄	1m	3a	4n	63	95:5

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