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Iron(II)-Catalyzed Sulfur Directed C(sp³)-H Bonds Amination/C-S Cross Coupling

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An efficient Iron(II)-catalyzed sulfur directed $C(sp^3)$ -H bonds amination/C-S cross coupling reaction has been developed. The reaction was with high tolerance of functional groups under the moderate condition. The results of deuterium labeling study and *in situ* ESI-MS experiments indicate that the reaction mechanism probably through a Fe(II)/Fe(III) catalytic cycle.

As one of the most important organic compounds, sulfocompounds were widely applied in synthesis, pharmaceutical and functional material.¹ Due to bigger atomic radius and higher electron density, sulfur has more activate pattern and easy modification in theoretically.² Recently sulfur directed C-H bond functionalization has made some progress.³ However, compare to the state art of oxygen directed and nitrogen directed, sulfur directed C-H bonds functionalization was rarely been studied. The mainly reason sulfur is very susceptible deactivate the transition metals.⁴ Developed more efficiently strategy of sulfur directed C-H functionalization is still in highly desirable.

Comparative to the C(sp)-H and C(sp²)-H, the C(sp³)-H bond functionzlizations need more harsh conditions and activated reaction systems.⁵ Considering the significance of diversifying synthetic strategies, we focused our interest on the sulphur directed C-H bond functionizationals.⁶ Herein, we report a novel Fe(II)-catalyzed sulfur directed C(sp³)-H bonds amination/C-S cross coupling reaction. In this reaction, the inactive C(sp³)-H bonds were smoothly direct amination under a moderate condition. At last, the reaction mechanism was studied by the deuterium labeling study and *in situ* ESI-MS experiments.

The reaction conditions were screened based on a model reaction of phenylmethanethiol (1a) and 2-iodobenzenamine (2a) (Table 1). $Fe(OAc)_2$ exhibited superior efficiencly catalytical over all examined Fe salt (entries 1-5). It was discovered that LS was the ideal catalyst (entries 5-12). Cs_2CO_3 turned out to be the

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proper base (entries 12-15). Either the reaction temperature was lower or higher than 100°C, the corresponding product yield was decreased (entries 16-17). Thus, the optimum reaction condition was determined as the entry 8.

Table 1. Optimization of the reaction conditions.^a

1a	SH +		Fe salt, Ligand CO ₃ , DMSO, 100	
intry	Ligand	Fe salt	Base	Yield (%) ^b
	L1	FeCl ₂	Cs_2CO_3	0
2	L1	FeBr ₂	Cs_2CO_3	0
5	L1	FeSO ₄	Cs_2CO_3	23
Ļ	L1	FeCl ₂	Cs_2CO_3	19
5	L1	Fe(OAc) ₂	Cs ₂ CO ₃	38
5	L2	Fe(OAc) ₂	Cs_2CO_3	29
,	L3	Fe(OAc) ₂	Cs_2CO_3	36
8	L4	Fe(OAc) ₂	Cs_2CO_3	86
)	L5	Fe(OAc) ₂	Cs_2CO_3	46
.0	L6	Fe(OAc) ₂	Cs_2CO_3	38
.1	L7	Fe(OAc) ₂	Cs_2CO_3	67
.2	L8	Fe(OAc) ₂	Cs_2CO_3	38
.3	L5	Fe(OAc) ₂	Na ₂ CO ₃	0
.4	L5	Fe(OAc) ₂	K ₂ CO ₃	42
.5	L5	Fe(OAc) ₂	K ₃ PO ₄	31
.6	L5	Fe(OAc) ₂	Cs ₂ CO ₃	35 ^c
.7	L5	Fe(OAc) ₂	Cs_2CO_3	49 ^{<i>d</i>}
	R		R ²	
	L1: R ¹ = H L2: R ¹ = CI L3: R ¹ = OH L4: R ¹ = OCH ₃		L5: R ² = H L6: R ² = CI L7: R ² = OH L8: R ² = OCH ₃	

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⁺ Footnotes relating to the title and/or authors should appear here.

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^{*a*} Unless otherwise noted, reactions conditions were **1a** (0.3 mmol), **2a** (0.3 mmol), Fe salt (5 mol%), ligand (5 mol%), base (2 equiv), DMSO (4 mL), 100 °C for 24 h. ^{*b*} Isolated yield. ^{*c*} 90 °C. ^{*d*} 110 °C.

Next, the reaction scope was been screened, a wide array of phenylmethanethiols **1** and 2-iodobenzenamines **2** were subjected to this reaction and given the products in good to excellent yields (Table 2). It was found that both the electron-donating and electron-withdrawing phenylmethanethiols derivatives reacted smoothly with 2-lodobenzenamines **2**. Phenylmethanethiols **1** bearing electron-donating groups showed better activity than bearing electron-withdrawing groups. 2-lodobenzenamines **2** bearing electron-withdrawing groups. Despite the electron-withdrawing effect of trifluoromethyl group is so strong, the corresponding product **3f** was still obtained in 72% yield (entry 5).

Table 2. Fe(II)-catalyzed sulfur directed C-H amination/C-S cross coupling.^a



 o Reactions conditions: 1 (0.3 mmol), 2 (0.3 mmol), Fe(OAc)_2 (5 mol%), L5 (5 mol%), Cs₂CO₃ (2 equiv), DMSO (4 mL), 24 h. b Isolated yields.

Furthermore, 2-bromobenzenamines with 4 phenylmethanethiols 1 were also successfully the given corresponding products (Table electron-deficient 3). The phenylmethanethiols 1 were successfully afforded the corresponding product (entries 4-6)





 $[^]a$ Reactions conditions: 1 (0.3 mmol), 4 (0.3 mmol), Fe(OAc)_2 (5 mol%), L5 (5 mol%), Cs₂CO₃ (2 equiv), DMSO (4 mL), 24 h. b Isolated yields.

To obtain the preliminary data of the mechanism, some addition reactions were been done (Scheme 2). At first, the model reaction (Scheme 2I) was conducted in two separate steps: the C-S cross coupling reaction of **1a** with **2a** given a product **6** (Scheme 2II). Next, **6** was reacted under our standard conditions, the reaction successfully obtained the target product **3a** in 81% yield (Scheme 2III), indicating that an intermediate **6** was involved in the reaction mechanism.



I 1a (0.3 mmol), 2a (0.3 mmol), Fe(OAc)₂ (5 mol%), L5 (5 mol%), Cs₂CO₃ (2 equiv). II 1a (0.5 mmol), 2a (0.5 mmol), KF/Al₂O₃ (2 equiv), CuI (10 mol%), H₂O (4 mL), 100 °C. III 6 (0.3 mmol), Fe(OAc)₂ (5 mol%), L5 (5 mol%), Cs₂CO₃ (2 equiv).

Scheme 1.

Additionally, the model reaction mixture⁷ was subjected to the *in situ* ESI-MS analysis which the detection temperature was enacted at 120 °C (Scheme 3a).⁸ The positive-ion mode ESI-MS showed a peak at 459.1 (m/z) which corresponding to $[L_2FeH]^+$. The peak at 550.2 was assigned to $[L_2FePhNH_2]^+$. And, the peak at 674.2 and 690.2 were assigned to $[L_2FePh_2CH_2SNH_2H]^+$ and $[L_2FePh_2CH_2SNH_2O_2H]^+$, respectively. Meanwhile, using the deuterium labeling study also further validated the intermediate components hypothesis (Scheme 3b).⁸



Scheme 2. The *in suit* ESI-MS spectras of Fe(II)-catalyzed sulfur directed C-H amination/C-S cross coupling.

Based on the above results, the reaction mechanism was proposed (Scheme 4). After the coordination of Fe(OAc)₂ with L5, the corresponding intermediate 7 was generated.⁹ Next, a Fe(III) intermediate 8 was formed by the oxidative addition of 7 with 2haloaniline. Next, 8 reacted with phenylmethanethiol produced intermediate 9 by ligands exchange step. Subsequently, 9 afforded the key intermediate 10 by an intermolecular oxidative addition. Finally, 10 furnished the desired products 3 through reductive elimination step, and meanwhile concomitantly generated the intermediate 7 which re-entered the catalytic cycle.



Scheme 3. Proposed mechanism.

Conclusions

In conclusion, we have developed a Fe(II)-catalyzed sulfur directed $C(sp^3)$ -H bonds amination/C-S cross coupling reaction. The reaction was with high tolerance of functional groups

under the moderate condition. The results of deuterium labeling study and *in situ* ESI-MS experiments indicate that that the catalytic reaction probably through a Fe(II)/Fe(III) catalytic cycle.

Notes

General procedure for preparation of 3 and 5

A mixture of phenyl-methanethiol **1a** (0.3 mmol, 37.2 mg), 2-lodophenylamine **2a** (0.3 mmol, 65.7 mg), Fe(OAc)₂ (5 mol%, 8.7 mg), 2-(2-Dimethylamino-vinyl)-inden-1-one **L5** (5 mol%, 10.0 mg) and Cs₂CO₃ (2 equiv, 195.6 mg) in DMSO (4 mL) was stirred under a N₂ atmosphere. After the reaction mixture was stirred at 100 °C for 24 h, it was allowed to cool to ambient temperature. Then the mixture was quenched with saturated salt water (10 mL), and the solution was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined and dried by sodium sulfate and concentrated in vacuo. The pure product 2-Phenyl-benzothiazole **5a** (54.4 mg, 86% yield) was obtained by flash column chromatography on silica gel.

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