

Copper bis(2,2,6,6-tetramethyl-3,5-heptanedionate) catalyzed synthesis of N-substituted ferrocenes

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Abstract

An efficient catalytic protocol for the Ullmann-type coupling reaction of both bromo and iodoferrocene with heterocyclic amines using a stable and well defined copper bis(2,2,6,6-tetramethyl-3,5-heptanedionate) complex has been developed. The protocol was applicable for the synthesis of wide variety of N-substituted ferrocenes and the desired products were obtained in good to excellent yields.

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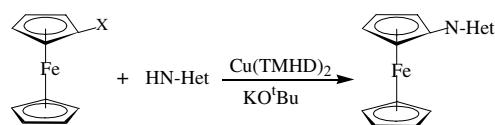
Keywords: Ferrocene; Heterocycle; Cross coupling; Ullmann coupling

In recent years, the applications of ferrocenes and their derivatives have been widespread in many fields of chemistry¹ such as material science,² asymmetric catalysis³ and biologically active compounds.⁴ Although ferrocenes are classical aromatic compounds, standard methods for derivatization of aromatics may not work for ferrocene due to its specific electronic and geometric properties. Owing to its unique properties the synthesis of N-substituted ferrocene has been rarely explored. These compounds are typically synthesized in several steps by the introduction of amino group in ferrocene followed by its derivatization.^{5,6} In 1981, Sato and its coworkers reported the synthesis of N-ferrocenyl phthalimide in the presence of copper(I) oxide and pyridine.⁷ Later on, Herberhold et al. reported the synthesis of ferrocenyl amines from ferrocenyl bromide and sodium amides.⁸ Recently, the direct synthesis of N-substituted ferrocenes using stoichiometric amount of CuI in DMSO has been reported.⁹ However, most of these reactions require stoichiometric amount of copper salts that makes scale up unfeasible and does not work for the coupling of less reactive bromo ferrocene. Hence, there is a need to develop an efficient catalytic protocol applica-

ble for the synthesis of wide variety of N-substituted ferrocenes.

In continuation of our work on the synthesis of ferrocene derivatives and C–N coupling reactions,¹⁰ we herein report coupling of both bromo and iodoferrocene with heterocyclic amines by a stable and well defined copper bis(2,2,6,6-tetramethylheptanedionate) [Cu(TMHD)₂] complex. The ease of preparation of the complex,¹¹ its high solubility in organic solvents, indefinite shelf life, stability towards air and compatibility with various hindered and functionalized heterocycles makes it an ideal catalyst for coupling of iodo and bromoferrocene with heterocyclic amines. (Scheme 1).

To evaluate the effect of catalyst, solvent and base, the coupling of indole with iodoferrocene was selected as a model reaction. Initially the catalytic activity of various β-diketonate complexes such as Cu(TMHD)₂, copper bis(acetylacetonate) Cu(acac)₂, copper bis(ethylacetoacetate)



X = I, Br HN-Het = indoles, pyrazole, pyrrole, imidazole, benimidazole, triazole.

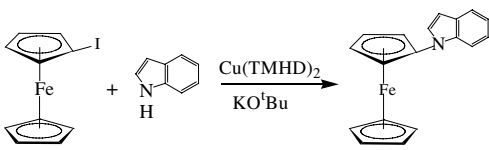
Scheme 1. Synthesis of N-substituted ferrocenes.

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$\text{Cu}(\text{eaa})_2$, nickel bis(2,2,6,6-tetramethyl-3,5-heptanedionate) $\text{Ni}(\text{TMHD})_2$ and iron bis(2,2,6,6-tetramethyl-3,5-heptanedionate) $\text{Fe}(\text{TMHD})_2$ were investigated (Table 1). The results show that $\text{Cu}(\text{TMHD})_2$ was the best catalyst and the probable reason may be that there exist a better balance between the electronic and steric effects in the $\text{Cu}(\text{TMHD})_2$ complex. The effect of various solvents like toluene, DMSO, DMF, NMP and dioxane on the reaction system was investigated and toluene was found to be a better solvent. Out of various bases like NaOMe, K_2CO_3 , K_3PO_4 , Cs_2CO_3 , KO^tBu and KOH, KO^tBu was found to be the most effective providing high yield and the probable reason may be due to the higher solubility of KO^tBu in organic solvents.

To study the generality of the procedure, a series of N-substituted ferrocenes having different steric and electronic properties were synthesized using $\text{Cu}(\text{TMHD})_2$ as catalyst under optimized conditions (Table 2, entries 1–16). Indole with electron donating and withdrawing substituents was found to couple smoothly both with iodo and less reactive bromoferrocene providing moderate to good yield of the desired products (entries 1–6).¹² Also, no significant electronic and steric effects were observed for 2 and 5 substituted indoles under the present catalytic system. Pyrrole also reacted efficiently with iodoferrocene, while the reaction was found to be sluggish with bromoferrocene (entries 9 and 10). The arylation of pyrazole, imidazole, benzimidazole and triazole was also studied and required the use of a polar solvent like DMSO due to poor solubility of these substrates in toluene. Pyrrole reacted smoothly with iodo and bromo ferrocene providing good to excellent yield of the desired product (entries 7 and

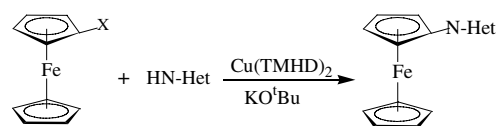
Table 1
Effect of catalysts under different reaction conditions for the synthesis of N-ferrocenylinole^a



| Entry | Solvent | Catalyst | Base | Yield (%) |
|-------|---------|----------------------------|-------------------------|-----------|
| 1 | Toluene | $\text{Cu}(\text{TMHD})_2$ | KO ^t Bu | 96 |
| 2 | Toluene | $\text{Cu}(\text{acac})_2$ | KO ^t Bu | 20 |
| 3 | Toluene | $\text{Cu}(\text{eaa})_2$ | KO ^t Bu | 12 |
| 4 | Toluene | $\text{Ni}(\text{TMHD})_2$ | KO ^t Bu | — |
| 5 | Toluene | $\text{Fe}(\text{TMHD})_2$ | KO ^t Bu | — |
| 6 | DMSO | $\text{Cu}(\text{TMHD})_2$ | KO ^t Bu | 72 |
| 7 | DMF | $\text{Cu}(\text{TMHD})_2$ | KO ^t Bu | 45 |
| 8 | NMP | $\text{Cu}(\text{TMHD})_2$ | KO ^t Bu | 21 |
| 9 | Dioxane | $\text{Cu}(\text{TMHD})_2$ | KO ^t Bu | 10 |
| 10 | Toluene | $\text{Cu}(\text{TMHD})_2$ | NaOMe | 70 |
| 11 | Toluene | $\text{Cu}(\text{TMHD})_2$ | K_2CO_3 | 68 |
| 12 | Toluene | $\text{Cu}(\text{TMHD})_2$ | K_3PO_4 | 46 |
| 13 | Toluene | $\text{Cu}(\text{TMHD})_2$ | KOH | 18 |

^a Reaction conditions: iodoferrocene (2 mmol); indole (2.2 mmol); catalyst (10 mol %); base (4 mmol); solvent (10 ml); temperature 120 °C; reaction time 12 h.

Table 2
Synthesis of various N-substituted ferrocenes catalyzed by $\text{Cu}(\text{TMHD})_2$ ^a


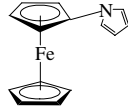

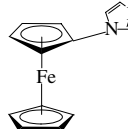

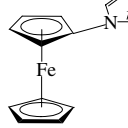

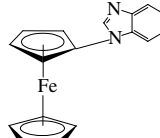

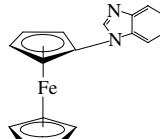

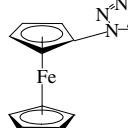

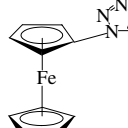


X = I, Br
HN-Het = indoles, pyrazole, pyrrole, imidazole, benzimidazole, triazole.

| Entry | Heterocyclic amine | Product | Yield ^e (%) |
|--------------------|--------------------|---------|------------------------|
| 1 ^c | | | 95 |
| 2 ^{b,c,d} | | | 61 |
| 3 ^{b,c} | | | 88 |
| 4 ^{b,c,d} | | | 52 |
| 5 ^b | | | 68 |
| 6 ^{b,d} | | | 30 |
| 7 | | | 96 |
| 8 ^{b,d} | | | 80 |
| 9 ^{b,c} | | | 74 |

(continued on next page)

Table 2 (continued)

| Entry | Heterocyclic amine | Product | Yield ^c (%) |
|---------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------|
| 10 ^{b,c,d} |  |  | 34 |
| 11 |  |  | 46 |
| 12 ^{b,d} |  |  | 22 |
| 13 ^b |  |  | 35 |
| 14 ^{b,d} |  |  | 18 |
| 15 |  |  | 28 |
| 16 ^{b,d} |  |  | 14 |

^a Reaction conditions: iodoferrocene (2 mmol); heterocyclic amine (2.2 mmol); Cu(TMHD)₂ (10 mol %); KO^tBu (4 mmol); DMSO (10 ml); temperature 90 °C; reaction time 12 h.

^b Cu(TMHD)₂ 20 mol %.

^c Toluene as solvent at 120 °C.

^d Bromoferrocene (2 mmol); time 36 h.

^e Isolated yield.

8). *N*-Ferrocenyl derivatives of imidazole, benzimidazole and triazole (entries 11–16) were also synthesized easily, as they are the compounds of synthetic interest and are usually prepared by the derivatization of ferrocenyl amine.

In summary, an efficient catalytic protocol for the synthesis of *N*-substituted ferrocenes using stable and well defined Cu(TMHD)₂ complex is reported for the first time. The catalytic system is capable of coupling both iodo and less reactive bromo ferrocene with heterocyclic amines providing modest to excellent yield of the desired products.

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- Typical procedure for the preparation of Cu(TMHD)₂*: NaOH (22 mmol) was dissolved in methanol (20 ml) with stirring and the resulting solution was cooled to room temperature followed by the addition of TMHD (20 mmol). To the mixture, a solution obtained by dissolving Cu(NO₃)₂·6H₂O (10 mmol) in 20 ml methanol was added over a period of 30 min. The reaction mixture was stirred for 6 h and the resulting precipitate was filtered and dried. Mp 196–198 °C.

General procedure of Cu(TMHD)₂ catalyzed synthesis of N-ferrocenylindole: Under nitrogen atmosphere, iodoferrocene (2 mmol), indole (2.2 mmol), Cu(TMHD)₂ (10 mol %) and KO^tBu (4 mmol) were added in toluene (5 ml) and stirred at room temperature. The reaction mixture was then heated in a preheated oil bath at 120 °C for 12 h. The reaction mixture was then cooled to room temperature and solvent was removed under reduced pressure. The residue obtained was then purified by column chromatography (silica gel, 60–120 mesh) using petroleum ether (60:80)/ethyl acetate as an eluent to obtain the pure product.

Physical and spectral data of selected products:

N-Ferrocenyl-2-methylindole (Table 1, entry 3): mp 118–120 °C; IR (KBr): $\nu_{\max}/\text{cm}^{-1}$ 1555, 1454, 1311, 1104, 815, 747; ¹H NMR (400 MHz; CDCl₃): δ 2.46 (s, 3H, CH₃), 4.25–4.26 (m, 2H, C₅H₄), 4.29–4.30 (m, 5H, C₅H₅), 4.58 (m, 2H, C₅H₄), 6.31 (s, 1H, CH), 7.10–7.14 (m, 1H, C₆H₄), 7.20–7.23 (m, 1H, C₆H₄), 7.50 (d, 1H, C₆H₄), 8.25 (d, 1H, C₆H₄). ¹³C NMR 15.04, 29.88, 63.85, 65.12, 69.66, 96.23, 102.80, 112.51, 119.70, 120.09, 128.72, 132.79, 137.6, 143.12. MS (EI 70 eV): 315 (M⁺), 235, 180, 152, 121, 56.

N-Ferrocenyl-5-nitroindole (Table 1, entry 5): mp 114–116 °C; IR (KBr): $\nu_{\max}/\text{cm}^{-1}$ 1503, 1435, 1340, 1232, 834, 738, 502; ¹H NMR (400 MHz; CDCl₃): δ 4.26–4.27 (m, 2H, C₅H₄), 4.28–4.29 (m, 5H, C₅H₅), 4.65 (m, 2H, C₅H₄), 6.74 (d, 1H, CH), 7.57 (d, 1H, NCH), 7.7 (d, 1H, C₆H₃), 8.11–8.14 (dd, 1H C₆H₃), 8.58 (d, 1H C₆H₃). ¹³C NMR 29.85, 63.47, 66.24, 69.65, 96.23, 104.95, 110.99, 118.30, 128.68, 132.58, 139.67, 142.12 MS (EI 70 eV): 346 (M⁺), 235, 180.

N-Ferrocenylbenzimidazole (Table 1, entry 13): mp 106–108 °C; IR (KBr): $\nu_{\text{max}}/\text{cm}^{-1}$ 3084, 1508, 1237, 1109, 1001; ^1H NMR (400 MHz; CDCl_3): δ 4.27 (m, 2H, C_5H_4), 4.28–4.29 (m, 5H, C_5H_5), 4.66 (m, 2H, C_5H_4), 7.25 (s, 1H, CH), 7.31–7.36 (m, 1H, C_6H_4), 7.71 (d, 1H, C_6H_4),

7.83 (d, 1H, C_6H_4) 8.16 (d, 1H C_6H_4), 8.58 (d, 1H, C_6H_4). ^{13}C NMR 29.84, 62.87, 66.36, 69.80, 93.62, 111.38, 120.74, 128.67, 132.67, 137.85, 143.40. MS (EI 70 eV): 302 (M^+), 235, 180, 118, 121, 56.