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N-Arylation of aliphatic, aromatic and heteroaromatic amines catalyzed by copper bis(2,2,6,6-tetramethyl-3,5-heptanedionate)

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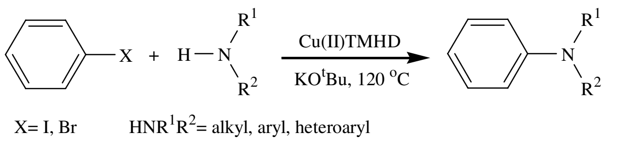
Abstract—Copper bis(2,2,6,6-tetramethyl-3,5-heptanedionate) was found to be an efficient catalyst for N-arylation of aliphatic, aromatic and heteroaromatic amines with aryl iodides/bromides under mild conditions. The system tolerated a variety of hindered and functionalized amines/aryl halides and the desired *N*-aryl amines were obtained in good to excellent yields.

The synthesis of *N*-aryl amines and *N*-aryl heterocycles is an active area in organic synthesis due to their occurrence in biologically important natural products, pharmaceuticals and their applications in materials research.[1] Among the various strategies developed to date, the copper-catalyzed Ullmann reaction has proven to be the most convenient synthetic route for installing an *N*-aryl functionality.[2] In addition, Buchwald[3] and Hartwig[4] have reported on Pd mediated C–N bond formation. However, copper-mediated couplings are still the reaction of choice for large and industrial scale formation of C–N bonds. The reaction system mostly employs an in situ generated catalyst from a copper source and highly efficient N/P-containing ligands such as amino acids,[5] diamines,[6] diimines,[7] pyridine,[8] oxime-phosphine oxides[9] and phosphoramidite.[10] In spite of the significant advances in this area, very few reports employing a structurally well defined and stable copper complex as a catalyst have been reported.[11] Another limitation is that, no single method has been successful for coupling aliphatic, aromatic and heteroaromatic amines with aryl halides. Thus, there is a need to develop a chemically well defined, stable solid metal complex, which could replace N or P-containing ligands and could directly catalyze the N-arylation of a wide range of weakly basic amines.

Thus in continuation of our work on C–N coupling reactions,[12] we herein report a facile N-arylation of aliphatic, aromatic and heteroaromatic amines catalyzed by a well-defined and stable complex, viz. copper bis (2,2,6,6-tetramethyl-3,5-heptanedionate) [Cu(II)-TMHD] as the catalyst in an efficient manner. The ease of preparation of the complex, its high solubility in organic solvents, indefinite shelf life, stability towards air and compatibility with various hindered and functionalized amines/aryl halides makes it an ideal complex for N-arylation of amines (Scheme 1).

Initially, various copper based β-diketonate complexes such as copper bis(2,2,6,6-tetramethyl-3,5-heptanedionate) [A], copper bis(acetyl acetonate) [B] and copper bis(methylacetoacetate) [C] were synthesized[13] and investigated for the amination of diphenylamine with iodobenzene in toluene at 120 °C (Table 1, entries 1–3). However, of these Cu-β-diketonate catalysts, only the Cu(II)TMHD complex was found to be effective providing an excellent yield of 95% of the desired



Scheme 1. N-arylation of aliphatic, aromatic and heteroaromatic amines with aryl halides.

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Table 1. Effect of catalyst on the N-arylation of diphenylamine with iodobenzene in toluene[a]

Entry	Complex	Base	Yield[b] (%)
1	A	KO^{t}Bu	95
2	B	KO^{t}Bu	35
3	C	KO^{t}Bu	—
4	A	NaOMe	10
5	A	K_2CO_3	—
6	A	KOH	5

[a] Reaction conditions: diphenylamine (2 mmol); iodobenzene (4 mmol); catalyst (20 mol %); KO^{t}Bu (4 mmol); toluene (10 ml); temperature 120 °C; reaction time 12 h.

[b] Isolated yield.

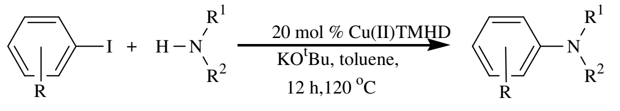
product. The reactivity trend could result from the fact that a better balance exists between the electronic and steric effects in the Cu(II)TMHD complex.

The influence of bases on the yield of triphenylamine (TPA) in the presence of Cu(II)TMHD as a catalyst was also investigated (Table 1, entries 1 and 4–6). It was found that KO^{t}Bu was the most effective base, while the use of other bases such as NaOMe, K_2CO_3 and KOH resulted in much lower or no yields. The probable reason for this may be due to the higher solubility of KO^{t}Bu in organic solvents.

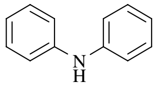
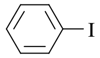
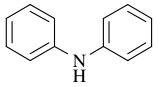
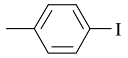
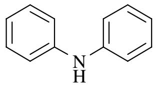
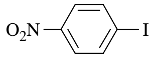
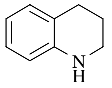
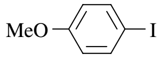
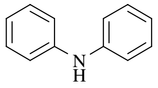
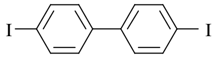
Thus, using Cu(II)TMHD as a catalyst, KO^{t}Bu as a base and toluene as solvent, various aliphatic, aromatic and heteroaromatic amines were coupled with aryl halides under mild conditions. Initially, the activity of Cu(II)TMHD was tested for the coupling of a secondary amine with iodobenzene leading to excellent yields of the desired products (Table 2, entries 1–5).[14] The protocol was successfully applied to couple electron rich aryl halides with diarylamine in high yields. The coupling of 4-iodonitrobenzene which is a difficult substrate (since it is dehalogenated easily to the corresponding arene) also proceeded smoothly under the present conditions (entry 3). Encouraged by the above results, double amination of diiodobiphenyl with diarylamine was also carried out and was found to proceed smoothly (entry 5). Thus, considerable rate enhancement along with an increased yield was observed for the N-arylation of secondary amines.

The scope of this methodology was further extended for coupling of primary amines with aryl iodides (Table 3, entries 1–6).[15] Substrates with varying degrees of substitution on both the reagents were examined and were found to provide triarylamines in good to excellent yields. Usually, primary amines give a mixture of secondary and tertiary amines, however, in the present case the coupling of anline with iodobenzene gave triphenylamine selectively in 94% yield (entry 1). A variety of functional groups including methyl, methoxy and trifluoromethyl were well tolerated. Also, no significant electronic and steric effects were observed for *meta* and *para* substituted substrates. The aliphatic amine benzylamine was also found to react smoothly under the present conditions (entry 6).

Table 2. N-arylation of secondary amines catalyzed by Cu(II)TMHD[a]



R= Me, OMe, NO_2 HNR^1R^2= alkyl, aryl

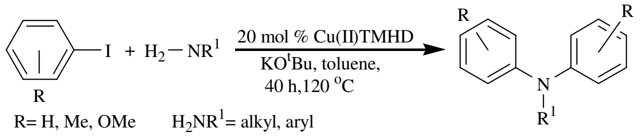
Entry	Secondary amine	Aryl halide	Yield[c] (%)
1			95
2			90
3			90
4			83
5[b]			81

[a] Reaction conditions: diaryl amine (2 mmol); aryl iodide (4 mmol); Cu(II)TMHD (20 mol %); KO^{t}Bu (4 mmol); toluene (10 ml); temperature 120 °C; reaction time 12 h.

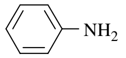
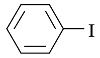
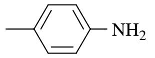
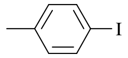
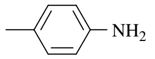
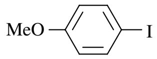
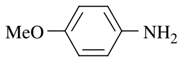
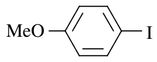
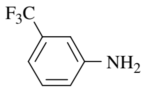
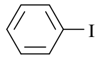
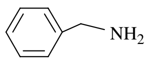
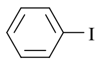
[b] Mole ratio of amine to halide 2.5:1.

[c] Isolated yield.

Table 3. N-arylation of primary amines catalyzed by Cu(II)TMHD[a]



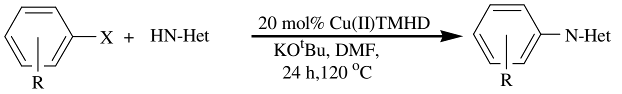
R= H, Me, OMe H_2NR^1= alkyl, aryl

Entry	Primary amine	Aryl halide	Yield[b] (%)
1			94
2			72
3			70
4			73
5			82
6			89

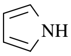
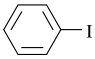
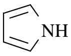
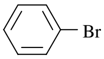
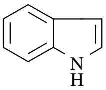
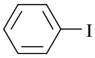
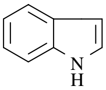
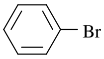
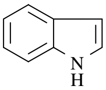
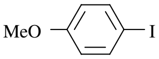
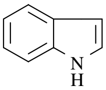
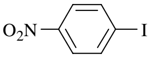
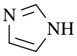
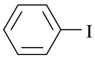
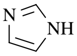
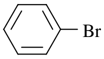
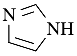
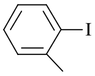
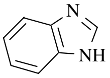
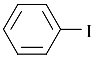
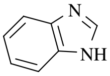
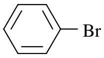
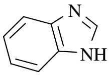
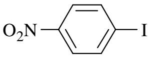
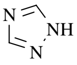
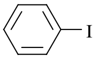
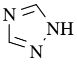
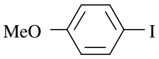
[a] Reaction conditions: primary amine (2 mmol); aryl iodide (8 mmol); Cu(II)TMHD (20 mol %); KO^{t}Bu (6 mmol); toluene (10 ml); temperature 120 °C; reaction time 40 h.

[b] Isolated yield.

Table 4. N-arylation of heteroaromatic amines catalyzed by Cu(II)TMHD[a]



X = I, Br, R= Me, OMe, NO_2 HN-Het = pyrrole, indole, imidazole, benzimidazole, triazole

Entry	Heterocycle	Aryl halide	Yield[d] (%)
1[b]			94
2[b]			88
3[c]			92
4[c]			88
5[c]			86
6[c]			87
7			92
8			90
9			74
10			90
11			70
12			74
13			51
14			46

[a] Reaction conditions: heteroaromatic (2 mmol); aryl halide (3 mmol); Cu(II)TMHD (20 mol %); KO^{t}Bu (4 mmol); DMF (10 ml); temperature 120 °C; reaction time 24 h.

[b] Toluene (10 ml) used as solvent.

[c] Aryl halide (4 mmol) was used.

[d] Isolated yield.

We next investigated this Cu(II)TMHD catalytic system and its tolerance to a wide range of heterocyclic compounds such as pyrrole, indole, imidazole, benzimidazole and triazole (Table 4, entries 1–14).[16] The arylations of indole, imidazole, benzimidazole and triazole required the use of a more polar solvent (DMF), most likely because of the poor solubility of these substrates in toluene. All the heteroaromatic compounds were effectively N-arylated with various aryl iodides in good to excellent yields. Successful coupling of these heterocyclic compounds with the less reactive aryl bromide was also carried out and afforded good yields of the desired products (entries 2, 4, 8 and 11). *ortho*, *meta* or *para* substituents on the aryl iodide were also tolerated. A variety of functional groups including methyl, methoxy and nitro on the aryl halide were viable partners under the present conditions.

In summary, the first example of the N-arylation of aliphatic, aromatic and heteroaromatic amines catalyzed by the Cu(II)TMHD-complex is described. This catalytic system is capable of coupling hindered substrates and tolerates a wide range of functional groups. Further work is in progress to broaden the scope of this catalytic system especially for aryl chlorides and to understand the reaction mechanism.

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References and notes

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13. Typical procedure for the preparation of Cu(II)TMHD: 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 2,2,6,6-tetramethyl-3,5-heptanedione (20 mmol). To the mixture, a solution obtained by dissolving $Cu(NO_3)_2 \cdot 6H_2O$ (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.
14. General procedure for the Cu(II)TMHD catalyzed N-arylation of secondary amines with aryl iodides: Under a nitrogen atmosphere, secondary amine (2 mmol), iodobenzene (4 mmol), Cu(II)TMHD (20 mol %) with respect to amine and KO^tBu (4 mmol) in toluene (10 ml) were stirred at room temperature. The reaction mixture was heated in an oil bath at 120 °C for 12 h. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue obtained was purified by column chromatography (silica gel, 60–120 mesh) using petroleum ether (60/80) as eluent to afford the pure product.
15. General procedure for the Cu(II)TMHD catalyzed N-arylation of primary amines with aryl iodides: Under a nitrogen atmosphere, primary amine (2 mmol), iodobenzene (8 mmol), Cu(II)TMHD (20 mol %) with respect to amine and KO^tBu (6 mmol) in toluene (10 ml) were stirred at room temperature. The reaction mixture was then heated in an oil bath at 120 °C for 40 h. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue obtained was purified by column chromatography (silica gel, 60–120 mesh) using petroleum ether (60/80) as eluent to afford the pure product.
16. General procedure for the Cu(II)TMHD catalyzed N-arylation of heteroaromatic amines with aryl iodides/bromides: Under a nitrogen atmosphere, heteroaromatic amine (2 mmol), aryl halide (3 mmol), Cu(II)TMHD (20 mol %) with respect to amine and KO^tBu (4 mmol) in DMF (10 ml) were stirred at room temperature. The reaction mixture was then heated in an oil bath at 120 °C for 24 h. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue obtained was purified by column chromatography (silica gel, 60–120 mesh) using petroleum ether (60/80)/ethyl acetate as eluent to afford the pure product.