An Efficient and Mild CuI/L-Proline-Catalyzed Arylation of Acetylacetone or Ethyl Cyanoacetate

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Abstract: The coupling reaction of aryl iodides with acetylacetone or ethyl cyanoacetate under catalysis of CuI/L-proline works at relatively mild conditions to provide 3-aryl-2, 4-pentanediones and α-aryl cyanoacetates in moderate to good yields.

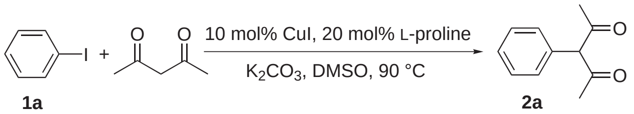
Key words: cross coupling, arylation, aryl iodide, catalysis, additive

Reaction of aryl halides with carbon nucleophiles, such as anions of active methylene compounds, is a useful tool for the preparation of substituted aromatic compounds,[1] such as 3-aryl-2,4-pentanediones and α-aryl cyanoacetates, which are very important building blocks for synthesizing various heterocycles, amino alcohols and amino acids.[2,3]

Among the many methods available for the α-aryl carbonyl compounds, a great deal of recent attention has focused on the development of palladium-catalyzed arylation methodology.[4] Some exciting achievements have already appeared in this field. For instance, the coupling of diethyl malonate or ethyl cyanoacetate with aryl chloride could be carried out at 70 °C using certain phosphines as the ligands.[4c] However, high costs and toxicity of Pd reagents and the relative ligands limit their application in industrial employment.

The arylation of activated methylene compounds mediated by copper salts is a well-established process,[5] but the reaction usually requires a stoichiometric amount of copper salt unless the halides are activated by an *o*-carboxylate group.[6] In 1993, Miura et al. reported a copper-catalyzed arylation of malononitrile, ethyl cyanoacetate and acetylacetone using aryl iodides.[7] However, their system required harsh condition (120 °C) and the substrate scope was limited. In recent years, research efforts in several laboratories have delivered a series of mild Ullmann-type methodologies based on employing some specific ligands. For examples, Buchwald and co-workers reported copper-catalyzed methods for arylation of amides, amines, N-heterocycles, hydrazides, phenols and α-aryl malonates using suitable additives such as glycol and diethylsalicyamide.[8] Ma's group discovered that L-proline and other amino acids were another type of effective ligands for copper-catalyzed coupling reactions of aryl halides with amines, N-heterocycles, sodium azide, sulfinic acid salts, phenols, and 1-alkynes.[9] Cristau and co-workers have also developed mild copper-catalyzed N-arylation and C-arylation by employing chelating Schiff base Chxn–Py–Al as the ligand.[10] Stimulated by their results, we recently found that L-proline could serve as a promoter for CuI-catalyzed coupling reaction of aryl iodides with acetylacetone or ethyl cyanoacetate, giving cross-coupling products in relatively mild conditions. Herein we wish to detail our results.

Initially, we used the reaction of iodobenzene with acetylacetone as a model to explore the suitable reaction conditions. It was found that under the conditions of 10 mol% CuI, 20 mol% L-proline, and 4 equivalents K_2CO_3 in DMSO the reaction gave 3-phenyl-2,4-pentanedione in 76% yield at 90 °C (Equation 1, entry 1 in Table 1). In the absence of L-proline, the reaction gave only 35% yield at 90 °C (entry 2), which indicated that the addition of L-proline is necessary to ensure a good yield. When the solvent was changed from DMSO to DMF, a low yield (17%) was obtained. Other additives were tested; *N*,*N*-dimethylglycine hydrochloride or *N*-methylglycine also worked but gave relatively low yields (46% for *N*,*N*-dimethylglycine hydrochloride, 53% for *N*-methylglycine).[a]



1a 2a

Equation 1

In order to explore the reaction scope, a number of aryl iodides with different substituents were tested and the results were summarized in Table 1. It was found that either electron-rich or electron-deficient aryl iodides were suitable for this reaction, giving desired coupling products in moderate to good yields. When 4-iodophenol was employed, the desired product was obtained only in 20% yield. It was possible that the self-coupling of 4-iodophenol made the reaction complex. The reaction of 3-iodoanisole gave a higher yield using Cs_2CO_3 as the base (entry 11 vs. entry 10). A few amount of benzyl methyl ketone as by-product was observed in some cases. It was noticed that the coupling of 1,3-cyclohexanedione with 4-iodoanisole gave a good result (entry 13) while it did not work in Buchwald's catalytic system.[8f]

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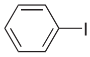
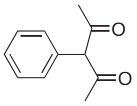
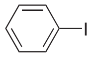
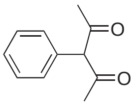
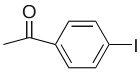
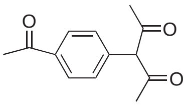
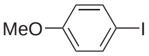
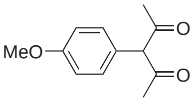
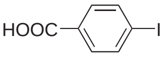
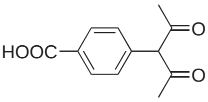
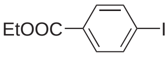
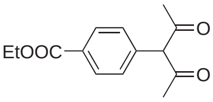
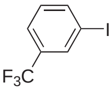
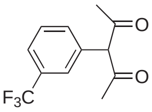
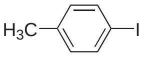
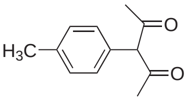
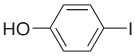
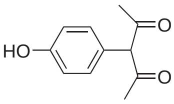
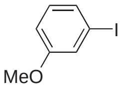
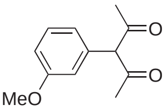
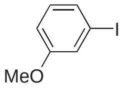
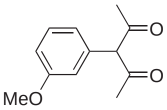
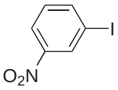
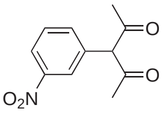
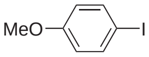
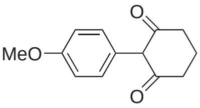
Table 1 CuI/L-Proline-Catalyzed Coupling Reaction of Aryl Iodides with Diketones[a]

Entry	Aryl iodide	Product	Temp (°C)/Time (h)	Yield (%)[b]
1			90/6	76
2			90/6	35[c]
3			90/14	73
4			90/20	56
5[d]			90/24	70
6			90/12	75
7			90/10	86
8			90/9	89
9			90/10	20
10			90/20	45
11[e]			60/20	66[f]
12[e]			60/24	79
13[g]			90/24	78

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[a] Reaction conditions: 0.5 mmol aryl iodide, 1.5 mmol acetylacetone, 0.05 mmol CuI, 0.1 mmol L-proline, 2 mmol K_2CO_3, DMSO, 90 °C.

[b] Isolated yield.

[c] L-Proline was not used.

[d] The amount of 2.5 mmol K_2CO_3 was used.

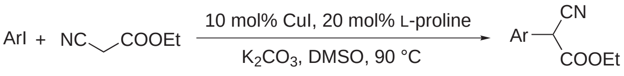
[e] Cs_2CO_3 was used as the base, and reaction was carried at 60 °C.

[f] Yield based on aryl iodide recovery.

[g] 1,3-Cyclohexanedione was used.

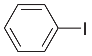
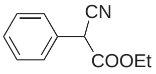
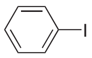
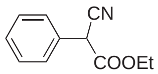
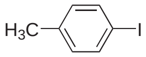
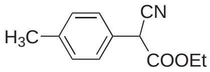
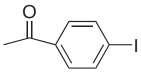
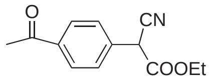
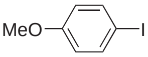
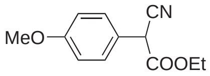
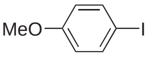
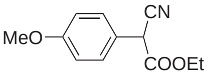
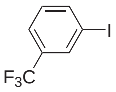
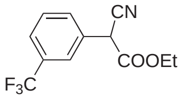
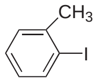
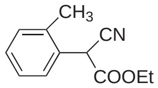
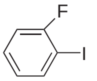
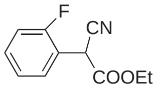
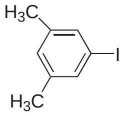
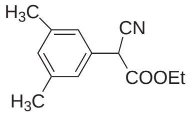
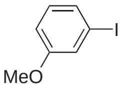
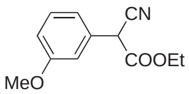
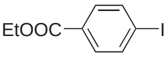
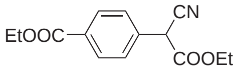
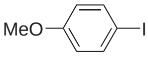
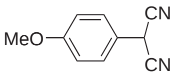
The ligand effect of L-proline on the coupling of aryl iodides with ethyl cyanoacetate was also confirmed. Under the promotion of L-proline, the reaction of iodobenzene with ethyl cyanoacetate gave a higher yield at 90 °C (Table 2, entry 1 vs. entry 2). When *N*,*N*-dimethylglycine hydrochloride or *N*-methylglycine was used as the additive, a relatively low yield (57% for *N*,*N*-dimethylglycine hydrochloride, 65% for *N*-methylglycine) was obtained. Further investigations indicated that a variety of aryl iodides, including those with fluoro, methoxy, carboxylate, and acetyl substituents, showed great ability to react with ethyl cyanoacetate in the presence of L-proline, providing

Table 2 CuI/L-Proline-Catalyzed Coupling Reaction of Aryl Iodides with Ethyl Cyanoacetate[a]



1

3

Entry	Aryl iodide	Product	Temp (°C)/Time (h)	Yield (%)[b]
1			90/5	67
2			90/5	47[c]
3			90/11	60
4			90/10	92
5			90/10	63
6			60/11	84[d]
7			90/12	78
8			90/19	37
9			90/13	67
10			90/13	78
11			90/14	69
12			90/12	80
13[e]			90/14	82

[a] Reaction conditions: 0.5 mmol aryl iodide, 1.5 mmol ethyl cyanoacetate, 0.05 mmol CuI, 0.1 mmol L-proline, 2 mmol K_2CO_3, DMSO, 90 °C.
[b] Isolated yield.
[c] L-Proline was not used.
[d] Cs_2CO_3 was used as the base, and reaction was carried at 60 °C.
[e] Malononitrile was used.

the corresponding coupling products (Table 2). Similar to the above-mentioned results, the use of Cs_2CO_3 as the base led to a higher yield for the reaction of 4-iodoanisole with ethyl cyanoacetate under milder conditions (entry 5 vs. entry 6). For the sterically hindered substrates, slightly low yields were observed (entry 8 and entry 9). The coupling of 4-iodoanisole with malononitrile also gave a good result (entry 13).

In summary, we have found that CuI/L-proline-catalyzed coupling reaction of aryl iodides with acetylacetone or ethyl cyanoacetate could be carried out at relatively mild conditions, which allows assembling 3-aryl-2,4-pentanediones or α-aryl cyanoacetates that possess a variety of functional groups in moderate to good yields. Further work on the coupling of less active aryl bromides or the replacement of the solvent by room temperature ionic liquids is in progress.

Typical Experimental Procedure

A mixture of iodobenzene (0.5 mmol), acetylacetone (1.5 mmol), K_2CO_3 (2.0 mmol), CuI (0.05 mmol), L-proline (0.1 mmol) in 2 mL of DMSO was heated at 90 °C under nitrogen atmosphere for 6 h. The cooled solution was poured into 1 N HCl, extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed to afford 3-phenyl-2, 4-pentanedione.

Acknowledgment

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