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Cu(I)/Diamine-catalyzed Aryl-alkyne Coupling Reactions

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Abstract: CuI/ethylene diamine/K_2CO_3/dioxane is shown to be a useful system for the cross coupling reactions of various aryl iodides and bromides with aryl and alkyl alkynes. Compared to the conventional Sonogashira reactions, the new procedure is free of palladium and phosphines.

Keywords: Sonogashira coupling reaction, CuI, aryl halide, alkyne, diamine.

Arylalkynes are important building blocks for the synthesis of natural products, pharmaceuticals, and artificial molecular devices[1]. They are often synthesized *via* the Pd-catalyzed Sonogashira coupling reactions between aryl halides and terminal alkynes[2,3]. Unfortunately, it remains difficult to apply the Sonogashira reaction to industrial scale and/or pharmaceutical synthesis, due to the high cost of Pd and the difficulty in removing the toxic Pd residues from the reaction products. Thus it is worthwhile to search for cheaper and less toxic catalysts for the aryl-alkyne couplings.

In 1992 Okuro *et al.* found that aryl halides can couple with terminal alkynes with CuI catalyst and Ph_3P ligand[4]. Wang *et al.* reported later that the CuI/Ph_3P-catalyzed aryl-alkyne coupling can also be performed under microwave irradiation[5]. Compared to the Sonogashira reactions, the CuI/Ph_3P-catalyzed aryl-alkyne coupling has advantage due to the low price of Cu. However, in Okuro and Wang's procedures the use of toxic Ph_3P is not desirable. Very recently Ma *et al.* discovered that CuI/N,N-dimethylglycine can catalyze the coupling of aryl halides with terminal alkynes[6]. Thus it is possible to achieve the Cu-catalyzed aryl-alkyne couplings with environmentally benign ligands.

Herein we decide to search for some other types of environmentally benign ligands for Cu(I)-catalyzed aryl-alkyne couplings. We are particularly interested in the N,N-bidentate ligands, because volatile or water soluble diamine ligands are easy to remove from the reaction mixture. Moreover, these ligands are usually inexpensive and valuable to the large and industrial scale synthesis[7]. Despite these advantages, study is few of the application of diamine ligands in the Cu-catalyzed aryl-alkyne coupling reactions[6].

In the beginning we focus on the coupling between PhI and phenylacetylene. A variety of experimental conditions are examined (See **Table 1**). The highest yield (89%) is obtained when 10 mol% CuI was used as the catalyst, 15 mmol% ethylene diamine as

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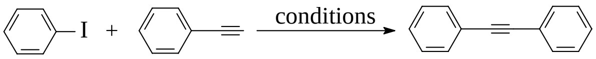
the ligand, K_2CO_3 as the base, and dioxane as the solvent. Other bases including K_3PO_4, pyridine, Et_3N, Cs_2CO_3, and Et_2NH, provided lower yields. Dioxane was found to be the best solvent, THF, toluene, and DMF cause lower yields. Furthermore, some other N,N-bidentate ligands including 2,2'-bipyridine, 1,10-phenanthroline and TMEDA are examined. Compared to ethylene diamine these ligands give lower yields[8].

Thus we conclude that the CuI/ethylene diamine/K_2CO_3/dioxane system is the optimal for the Cu(I)-catalyzed coupling reactions between aryl iodides and alkynes. Using the same procedure we then successfully coupled phenylacetylene with various substituted aryl iodides (see **Table 2**). The yields were 76-96%. Both the electron-withdrawing and donating substituents can be tolerated. Besides, oct-1-yne can also be coupled with various substituted aryl iodides. The yields are 87-96%. Therefore, the CuI/ethylene diamine/K_2CO_3/dioxane system can be used for the coupling reactions of aryl iodides with both aryl and alkyl alkynes.

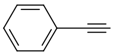
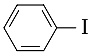
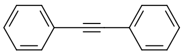
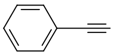
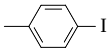
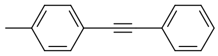
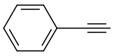
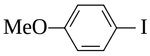
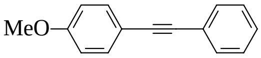
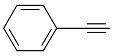
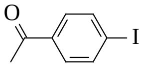
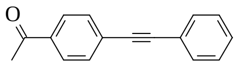
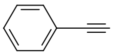
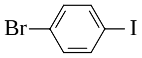
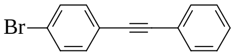
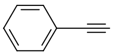
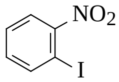
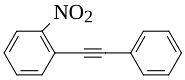
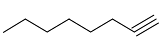
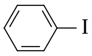
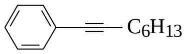
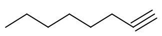
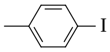
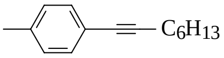
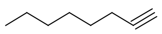
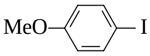
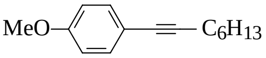
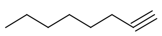
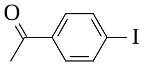
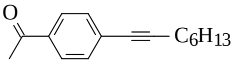
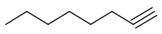
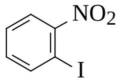
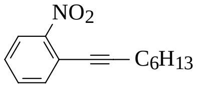
Table1 CuI-catalyzed coupling reaction between PhI and phenylacetylene under various condions[a]



Entry	Base	Ligand	Solvent	Temperature (°C)	Yield(%)[b]
1	K_2CO_3	$NH_2CH_2CH_2NH_2$	THF	75	12
2	K_3PO_4	$NH_2CH_2CH_2NH_2$	THF	75	8
3	K_2CO_3	$NH_2CH_2CH_2NH_2$	Toluene	110	40
4	K_3PO_4	$NH_2CH_2CH_2NH_2$	Toluene	110	72
5	K_2HPO_4	$NH_2CH_2CH_2NH_2$	Toluene	110	35
6	K_2CO_3	$NH_2CH_2CH_2NH_2$	DMF	120	59
7	K_3PO_4	$NH_2CH_2CH_2NH_2$	DMF	120	35
8	K_2CO_3	$NH_2CH_2CH_2NH_2$	Dioxane	100	89
9	K_3PO_4	$NH_2CH_2CH_2NH_2$	Dioxane	100	49
10	Pyridine	$NH_2CH_2CH_2NH_2$	Dioxane	100	13
11	Et_3N	$NH_2CH_2CH_2NH_2$	Dioxane	100	9
12	$^{i}Pr_2NH$	$NH_2CH_2CH_2NH_2$	Dioxane	100	17
13	Et_2NH	$NH_2CH_2CH_2NH_2$	Dioxane	100	11
14	Cyclohexylamine	$NH_2CH_2CH_2NH_2$	Dioxane	100	13
15	Cs_2CO_3	$NH_2CH_2CH_2NH_2$	Dioxane	100	57
16	K_3PO_4	2, 2′-Bipyridine	Dioxane	100	<5
17	K_2CO_3	2, 2′-Bipyridine	Dioxane	100	16
18	Et_3N	2, 2′-Bipyridine	Dioxane	100	<5
19	Et_2NH	2, 2′-Bipyridine	Dioxane	100	<5
20	K_3PO_4	1,10-Phenanthroline	Dioxane	100	31
21	K_2CO_3	1,10-Phenanthroline	Dioxane	100	15
22	K_3PO_4	TMEDA	Dioxane	100	7
23	K_2CO_3	TMEDA	Dioxane	100	<5

(a) Conditions: 10 mol% CuI, 15 mol% ligand, 5 mmol PhCCH, 6 mmol PhI, 20 mmol base, reaction time 24 h. (b) Isolated yield.

Table 2 CuI/$NH_2CH_2CH_2NH_2$-catalyzed couplings between alkynes and aryl iodides[a]

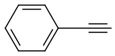
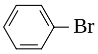
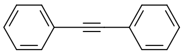
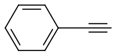
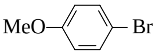
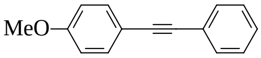
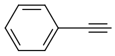
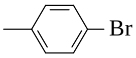
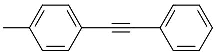
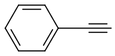
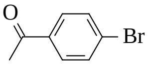
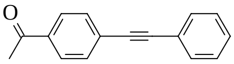
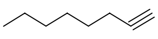
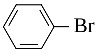
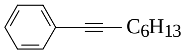
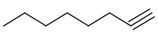
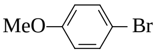
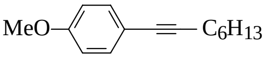
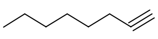
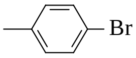
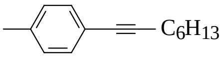
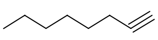
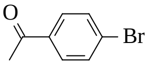
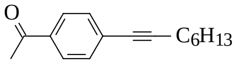
Entry	Alkyne	Aryl Iodide	Product	Yield (%)[b]
1				89
2				88
3				76
4				91
5				90
6				96
7				95
8				94
9				90
10				87
11				96

(a) General conditions: 10 mol% CuI, 15 mol% ethylene diamine, 5 mmol alkynes, 6 mmol aryl iodides, 20 mmol K_2CO_3 , reaction time 24 h, reaction temperature 100 °C. (b) Isolated yield.

Having examined aryl iodides, we next used the diamine ligands to couple alkynes with the less expensive aryl bromides. It was found that more CuI catalyst (see **Table 3**) was required for reasonable yields. Nonetheless, both the electron-withdrawing and donating substituents can be tolerated in the aryl bromides. Both aryl and alkyl alkynes can be utilized to generate the cross-coupling products.

In conclusion, the coupling reactions of aryl iodides and bromides with aryl and alkyl alkynes can be achieved using the CuI/ethylene diamine/K_2CO_3/dioxane system. The yields are about 90% for aryl iodides and 60-70% for aryl bromides. Compared to the conventional Sonogashira reactions, the new procedure is palladium free and phosphine free. Moreover, the ethylene diamine ligand in the reaction is remarkably cheap and easy to be removed and recycled. Thus we envisage that the new aryl-alkyne coupling method reported in the present study should be useful for large/industrial scale synthesis[9].

Table 3 CuI/$NH_2CH_2CH_2NH_2$-catalyzed couplings between alkynes and aryl bromides[a]

Entry	Alkyne	Aryl Bromide	Product	Yield (%)[b]
1				62
2				64[c]
3				60[c]
4				65
5				71
6				44
7				58[c]
8				60

(a) Conditions: 30 mol% CuI, 45 mol% $NH_2CH_2CH_2NH_2$, 5 mmol alkynes, 6 mmol ArBr, 15 mmol K_2CO_3, reaction time 24 h, temperature 110 °C. (b) Isolated yield. (c) KOH was used.

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References and Notes

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