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An efficient copper(I) complex catalyzed Sonogashira type cross-coupling of aryl halides with terminal alkynes

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ABSTRACT

A wide range of arylated alkynes are synthesized from the corresponding aryl halides and terminal alkynes through Sonogashira type cross-coupling reactions through C(aryl)–C bond formation in the presence of a catalytic amount of *N*,*N*′-dibenzyl BINAM–CuI complex under mild reaction conditions.

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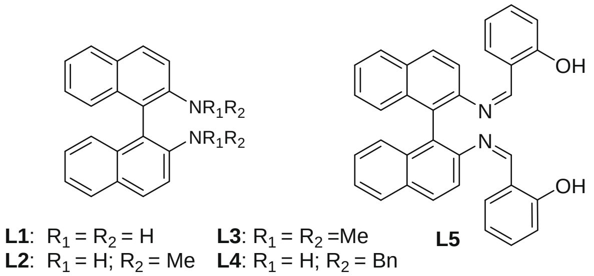
Acetylinic compounds constitute a very important class of organic compounds playing a significant role in a number of natural products and bioactive molecules.[1] Palladium-catalyzed synthesis of internal acetylenes from corresponding aryl halides and terminal acetylenes used to be the method of choice (Sonogashira coupling).[2] However, the high costs of palladium salts, requirement of copper as co-catalyst, high oxophillicity associated with phosphine ligands and tedious multistep processes involved in the synthesis of these phosphine ligands have rendered Pd unpopular, particularly for large scale reactions.



In order to overcome the drawbacks a great number of efforts have been directed to explore new catalytic systems recently.[3–5] Successful examples include the replacement of triphenylphosphine with some special phosphines to enhance the catalytic efficiency[3] and employing less expensive nickel instead of palladium.[4] However, the former suffers from the requirement of less conveniently available phosphines, while the latter still needs two metals, which makes catalyst recovery more difficult.

On the other hand, although it has been known for decades that aryl halides could couple with copper(I) acetylides to give aryl acetylenes,[6] there have been a few reports concerning the use of copper(I) alone as the catalyst for coupling of aryl halides with terminal alkynes.[7] Although in these reports copper is used as catalyst, high oxophillic phosphines are used as ligands.[7a–e,k] Later on, oxophillic phosphine ligands are replaced by nitrogen ligand to carry out the C–C bond forming Sonogashira coupling reaction.[7f–j] Recently, Sonogashira coupling reaction was carried out under microwave conditions using poly(ethylene glycol)s as solvent.[7h] Very recently, DABCO was used as ligand with CuI for the C–C bond formation between arylhalides and terminal alkynes.[7j] However, this advance in the field of Sonogashira coupling is not sufficient as most of the reactions need dry and oxygen free reaction conditions due to phosphine ligands and in some cases high catalytic loading (even super stoichiometric amounts of ligands are needed). Therefore a mild, economic and efficient catalytic system is still desirable for this process.

As a part of our ongoing research towards copper-catalyzed oxidation chemistry,[8] very recently we reported 1,1′-binaphthyl-2,2′-diamine (BINAM)[9]–Cu as an efficient catalyst for the synthesis of diaryl ethers and aryl alkyl ethers via Ullmann coupling.[10] In this

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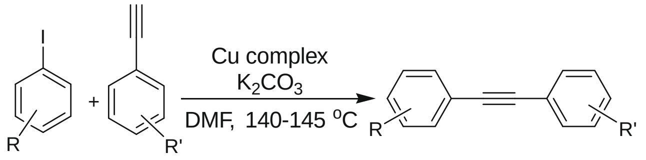


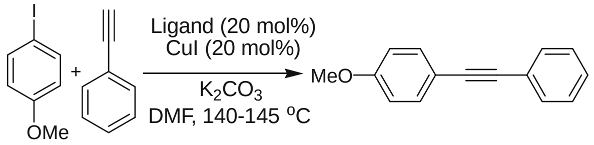
Scheme 1.

Letter we report our initial finding about easily available *N*,*N*′-dibenzyl BINAM–CuI complex catalyzed C(aryl)–C bond formation reaction (Sonogashira coupling) for the synthesis of internal alkynes from corresponding aryl halides and terminal alkynes (Scheme 1). This procedure is very simple, mild, clean and works efficiently without any additives.

In the preliminary studies, we used 20 mol % BINAM ligand **L1** with 20 mol % of CuI in the presence of K_2CO_3 (3 equiv) for the coupling of *p*-methoxy iodobenzene with phenyl acetylene in DMF at 140 °C. The reaction provided 85% isolated yield of the 1-methoxy-4-(phenylethynyl)benzene in 20 h through C(aryl)–C bond formation (Table 1, entry 1). When the ligand **L1** was replaced with ligand **L2**, the isolated yield was reduced to 45%. Replacing the ligand **L2** by **L3,** the yield was increased to 89%. Surprisingly, the *N*,*N*′-dibenzyl BINAM ligand **L4** with CuI catalyzed the Sonogashira cross-coupling reaction of *p*-methoxy iodobenzene with phenyl acetylene in DMF at 140 °C and provided quantitative yield for the expected product in just 6 h (entry 4). Usage of Salen ligand **L5** instead of **L4** provided only 76% yield in one day for the coupling reaction.

The reaction was screened with several copper salts, solvents and bases to increase the efficiency of the cross-coupling reactions and the results are summarized in Table 2. Although several copper salts catalyzed the coupling reaction, CuI and $Cu(OTf)_2$ turned out to be the copper salts of choice in view of yield as well as reaction time (Table 2, entries 1 and 2). The low cost of CuI over $Cu(OTf)_2$ encouraged us to proceed the coupling reaction with CuI. Similarly, DMF was the best solvent among those examined. K_2CO_3 was found to be the most effective base compared to Na_2CO_3 and Cs_2CO_3. Next, the reaction was carried out with different ratios of **L4** and CuI and it was found that 20 mol % of **L4**-copper combination was the most effective catalytic system. When the reaction was carried out only with CuI without **L4,** the reaction provided only 39% yield for the coupling reaction, which shows that ligand **L4** is mandatory for quantitative yield of the product.

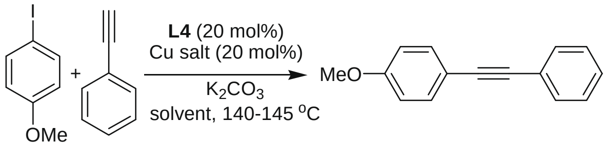
Table 1
CuI catalyzed Sonogashira coupling with different ligands



Entry	Ligand	Time (h)	Yield[a] (%)
1	**L1**	20	85
2	**L2**	24	45
3	**L3**	24	89
4	**L4**	06	99
5	**L5**	24	76

[a] Isolated yield.

Table 2
Effect of Cu salts, solvents and bases



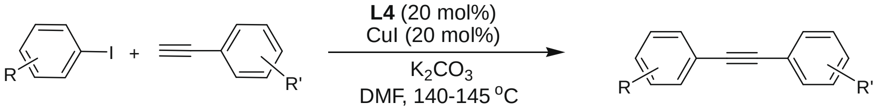
Entry	Cu salt	Solvent	Time (h)	Yield[a] (%)
1	CuI	DMF	06	99
2	$Cu(OTf)_2$	DMF	06	99
3	$Cu(OAc)_2$	DMF	24	92
4	$Cu(SO_4)_2\cdot 5H_2O$	DMF	24	72
5	CuBr	DMF	24	96
6	$CuCl_2\cdot 2H_2O$	DMF	24	91
7	CuCl	DMF	24	83
8	CuI	DMSO	24	85
9	CuI	MeCN	24	20[b]
10	CuI	Dioxane	24	29[b]
11	CuI	Xylene	24	00
12	CuI	Toluene	24	00[b]
13	CuI	DMF	24	46[c]
14	CuI	DMF	24	50[d]
15	CuI	DMF	24	23[e]

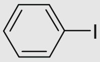
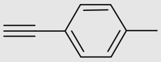
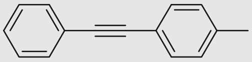
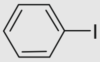
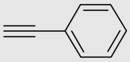
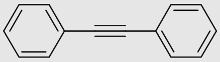
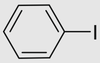
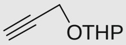
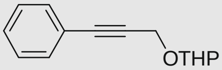
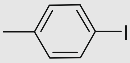
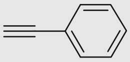
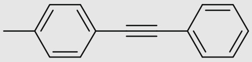
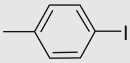
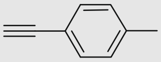
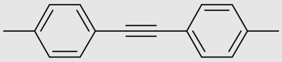
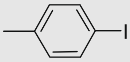
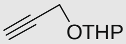
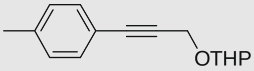
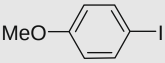
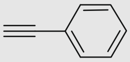
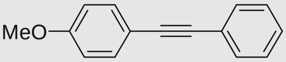
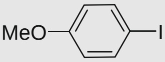
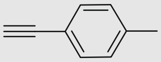
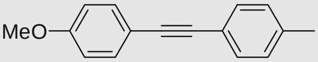
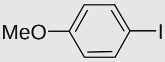
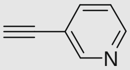
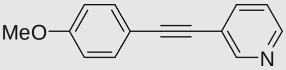
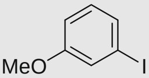
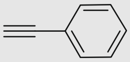
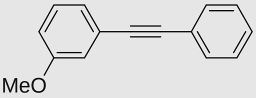
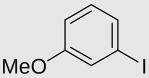
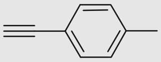
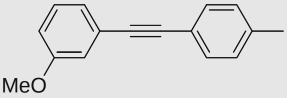
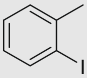
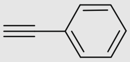
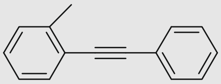
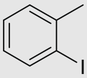
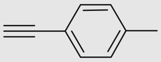
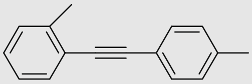
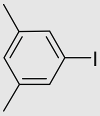
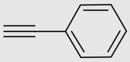
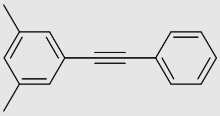
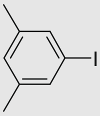
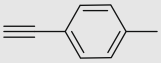
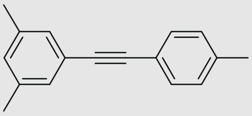
[a] Isolated yield.
[b] Reaction was carried out at boiling temperature of corresponding solvent.
[c] Na_2CO_3 was used as base.
[d] Cs_2CO_3 was used as base.
[e] K_3PO_4 was used as base.

Using the above-mentioned optimized conditions, we initiated our investigations into the scope of the *N*,*N*′-dibenzyl BINAM **L4**–CuI catalyzed Sonogashira type cross-coupling and the results are summarized in Table 3. Various aryl iodides and terminal alkynes reacted to give the corresponding arylated acetylenes. We found that iodobenzene containing electron-releasing groups such as methoxy group (entries 7–11) as well as electron-withdrawing group such as trifluoromethyl group (entries 20 and 21) reacted with terminal acetylenes to provide arylated alkynes in very high isolated yields. Highly sterically hindered *ortho*-substituted iodobenzenes also provided very good yields by reacting with terminal alkynes in the presence of **L4**–CuI complex (entries 16 and 17). The reaction condition tolerated acid sensitive functional groups. For example, OTHP ether containing terminal alkyne (2-(prop-2-ynyloxy)tetrahydro-2H-pyran) reacted with iodobenzene and *p*-methyl iodobenzene to provide corresponding arylated product in good yield without cleavage of acid sensitive -OTHP ether group (entries 3 and 6). Terminal alkyne containing heterocycle also reacted with aryl iodide in the presence of **L4**–CuI complex to provide corresponding arylated product in excellent isolated yield (entry 9). Under our optimized reaction conditions, aryl bromides also reacted with terminal alkynes to provide the corresponding C-arylated alkynes (entries 22–24). Using BINAM as ligand with copper has one advantage over other reported ligands as it can be used in enantiomerically pure form for the asymmetric Sonogashira coupling (non-enzymatic kinetic resolution) reaction.[11]

In summary, we have developed an efficient, and experimentally simple *N*,*N*′-dibenzyl BINAM–CuI complex catalyzed C-arylation of terminal alkynes with aryl iodides through C(aryl)–C bond formation reaction. Both the electron-releasing as well as electron-withdrawing groups containing aryl iodides react with terminal alkynes to provide arylated alkyne products in high yields. The reaction condition is very mild as OTHP ether is untouched during the entire reaction time. Efforts to expand the utility of our new catalyst to other class of nucleophiles will be reported in due course.

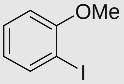
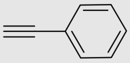
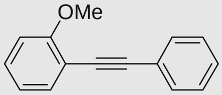
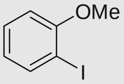
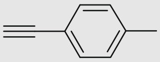
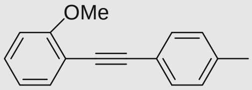
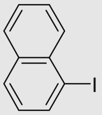
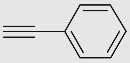
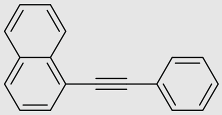
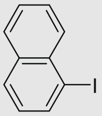
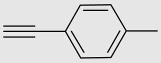
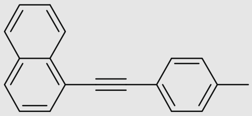
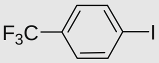
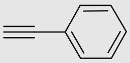
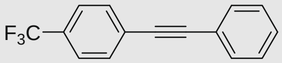
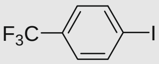
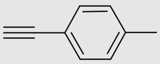
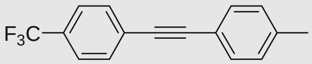
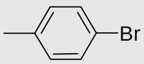
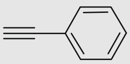
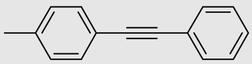
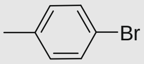
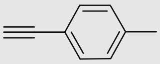
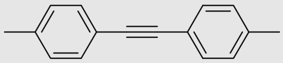
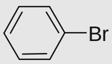
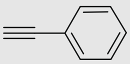
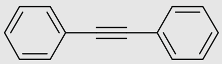
Table 3
Cross-coupling reaction of aryl halides with terminal alkynes in the presence of **L4**–CuI catalyst[a]



Entry	Aryl halide	Alkynes	Time (h)	Product[b]	Yield[c] (%)
1			20		75
2			6		90
3			20		75
4			6		79
5			20		88
6			20		73
7			6		99
8			24		72
9			24		70
10			14		77
11			20		93
12			8		99
13			24		96
14			14		94
15			20		99

(*continued on next page*)

Table 3 (*continued*)

Entry	Aryl halide	Alkynes	Time (h)	Product[b]	Yield[c] (%)
16			14		92
17			20		80
18			14		86
19			20		99
20			8		85
21			13		81
22			24		51
23			48		42
24			48		35

[a] 1.5 equiv of alkyne, 1 equiv of haloarene and 3 equiv of K_2CO_3 in 3 mL DMF was treated with 20 mol % of **L4**–CuI complex.

[b] All the alkynes gave satisfactory spectral data.

[c] Isolated yield.[12]

Acknowledgements

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12. *Typical representative experimental procedure*: *p*-methoxy iodobenzene (117 mg, 0.5 mmol), K_2CO_3 (207.3 mg, 1.5 mmol), *N,N′*-dibenzyl-BINAM

(46.4 mg, 0.1 mmol) and CuI (19 mg, 0.1 mmol) were taken in a 15 mL reaction tube capped with a septum. The reaction tube was evacuated and back-filled with nitrogen. DMF (3 mL) was added to the reaction mixture at room temperature and the resulting reaction mixture was heated to 140–145 °C. Phenyl acetylene (82.5 μL, 0.75 mmol) was added to the reaction mixture at 145 °C as two equal portions (41.3 μL) in 10 min intervals. The septum was replaced with a glass stopper and the reaction mixture was heated for 6 h (the progress of the reaction was followed by TLC). After complete disappearance of *p*-methoxy iodobenzene (TLC), the reaction mixture was allowed to cool to room temperature and the solvent was evaporated. The crude residue was directly purified by column chromatography on silica gel using ethyl acetate/hexane as the eluent to afford 1-methoxy-4-(phenylethynyl)benzene[7h] (103 mg, 99%) as a white solid; R_f 0.4 (in hexanes); FTIR (CH_2Cl_2): 1173, 1247, 2181, 2853, 2923, 2954 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 6.87 (dd, J = 7.2, 2 Hz, 2H), 7.27–7.39 (m, 3H), 7.42–7.56 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 88.2, 89.5, 114.2, 115.6, 123.8, 128.1, 128.5, 131.6, 133.2, 159.8; HRMS [M+1]$^+$ Calcd for $C_{15}H_{12}O$: 209.0966. Found: 209.0960.