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Bis(μ-iodo)bis((−)-sparteine)dicopper(I) catalyzed Sonogashira-type reaction under palladium and phosphine-free conditions

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ABSTRACT

An efficient and inexpensive protocol for the Sonogashira-type cross coupling reactions of phenylacetylenes with a variety of haloarenes including activated aryl chlorides employing the structurally well-characterized bis(μ-iodo)bis((−)-sparteine)dicopper(I) catalyst is described.

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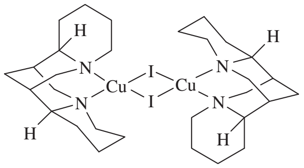
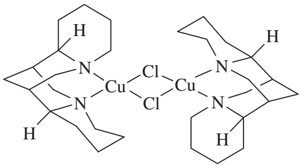
Aryl alkynes are important intermediates in pharmaceutical chemistry, natural products, and material science.[1–3] These compounds are often synthesized by the Sonogashira cross coupling reaction of terminal alkynes with aryl halides, employing palladium salts in conjunction with copper(I) iodide and phosphine ligands as catalytic systems.[3–5] The use of expensive palladium phosphine complexes with copper(I) iodide as co-catalyst, made palladium catalysts less useful, in particular, for industrial scale reactions. Therefore, it is highly attractive to perform such reactions under palladium and phosphine-free conditions. Recently, copper-catalyzed Sonogashira-type reaction of alkynes with aryl halides[6-16] has gained much attention owing to the lower toxicity and cost of copper salts. A number of phosphine and non-phosphine ligands, such as triphenylphosphine,[6] 1,10-phenanthroline,[7] ethylenediamine,[7c] *N*,*N*-dimethylglycine,[8] 1,4-diazabicyclo[2.2.2]-octane (DABCO),[9] 1,1'-binaphthyl-2,2'-diamine (BINAM) and its derivatives,[10] 1,1'-binaphthyl-2,2'-diol (rac-BINOL),[11] β-diketones,[12] pyrimidines,[13] salicylic acid,[14] 8-hydroxyquinoline[15] and *N*,*N*′-dimethylethylenediamine (DMEDA)[16] have been examined for copper-catalyzed Sonogashira-type coupling reactions. Most of these protocols employ either high loading of copper salts/ligands or they lack substrate generality. Moreover, it remains a challenging task to activate less reactive aryl halides, such as deactivated aryl bromides and chlorides for Sonogashira cross coupling reactions under palladium and phosphine-free conditions.

Generally the copper-catalyzed Sonogashira reactions are carried out using a catalyst generated in situ by combining the Cu source with the excess free ligands. Although these practices are quite useful in both small-scale and process chemistry operations, they suffer from many drawbacks; for example, an excess of ligand often inhibits the activity of the catalytic system and is not cost efficient, and the generation of the active species from the ligand and Cu source may also require an induction period or result in undesired side products due to the formation of metal complexes with different reactivity. Therefore, there is an increasing interest in using pre-formed copper complexes of different ligands as precatalysts.

Our group has recently shown that the use of the pre-formed dimeric copper complex [Cu_2I_2((−)-sparteine)$_2$] containing a $Cu_2(\mu\text{-}I)_2$ core coordinated by sterically hindered and poor σ-donor ligands, such as (−)-sparteine, in conjunction with CuI,



1



2

Figure 1. Bis(μ-halo)bis((−)-sparteine)dicopper(I) complexes.

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E-mail address: mlakshmi@iict.res.in (M.L. Kantam).

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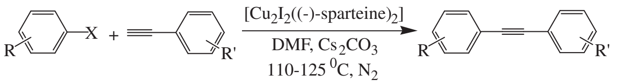
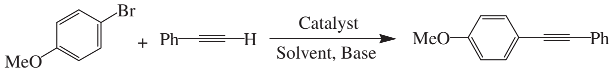


Scheme 1. Sonogashira-type cross coupling reaction with different aryl halides and alkynes.

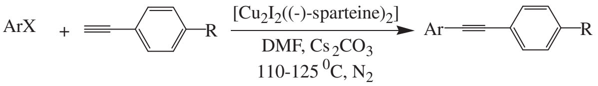
Table 1
Optimization of reaction conditions[a]

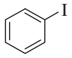
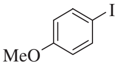
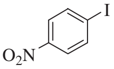
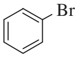
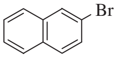
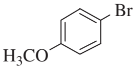
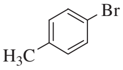
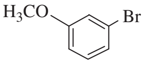
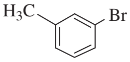
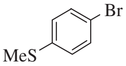
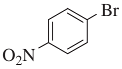
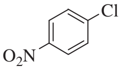
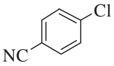
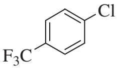
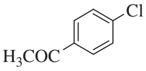
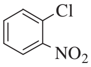
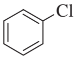
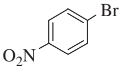
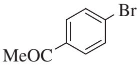
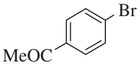
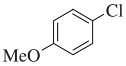
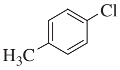


Entry	Catalyst	Solvent	Base	Yield[b] (%)
1	Cu_2O	DMSO	K_2CO_3	47
2	CuCl	DMSO	K_2CO_3	68
3	CuBr	DMSO	K_2CO_3	66
4	CuI	DMSO	K_2CO_3	80
5	CuI	DMSO	Cs_2CO_3	85
6	CuI	DMSO	KO^tBu	38
7	CuI	DMF	Cs_2CO_3	91
8	CuI	Toluene	Cs_2CO_3	70
9	$Cu_2I_2(spa)_2$	DMF	Cs_2CO_3	96[c]
10	$Cu_2Cl_2(spa)_2$	DMF	Cs_2CO_3	78[c]

[a] The reactions were carried out with bromoanisole (1 mmol), phenylacetylene (1.1 mmol), CuX (0.1 mmol, 10 mol %), (−)-sparteine (0.1 mmol, 10 mol %) and base (2 equiv) in 3 mL solvent at 125 °C under N_2 atmosphere.
[b] Isolated yields.
[c] Reactions performed with 5 mol % of pre-formed dimeric copper(I) complex.

Table 2
Sonogashira type cross coupling reactions of phenylacetylenes with various haloarenes catalyzed by bis(μ-iodo)bis((−)-sparteine)dicopper(I) (**1**)[a]



Entry	ArX	R	Temp (°C)	Time (h)	Yield[b] (%)
1		H	110	4	98
2		H	110	6	97
3		H	110	4	95
4		H	125	5	97
5		H	125	5	98
6		H	125	10	95
7		H	125	9	96
8		H	125	11	92
9		H	125	11	93
10		H	125	9	92
11		H	110	6	98
12		H	125	8	91
13		H	125	10	87
14		H	125	10	85
15		H	125	12	81
16		H	125	10	83
17		H	130	24	8, 15[c], 22[d]
18		F	125	12	92
19		OMe	125	10	90
20		OMe	125	12	97
21		H	130	24	5[c], 12[d]
22		H	130	24	6[c], 15[d]

[a] The reactions were carried our with $Cu_2I_2(spa)_2$ (1) (5 mol %), arylhalide (1 mmol), phenylacetylene (1.1 mmol), Cs_2CO_3 (2 equiv) in 3 mL DMF at the indicated temperature under N_2.
[b] Isolated yield.
[c] Reactions carried out with 10 mol % of catalyst.
[d] Reactions carried out with 20 mol % of catalyst.

catalyzes the direct N-arylation of NH-heterocycles with both sterically hindered and less reactive aryl halides.[17] Thus it was envisioned that the use of this pre-formed copper complexe of sparteine (Fig. 1) as the catalyst may result in good catalytic activities for C–C coupling reactions, in particular, with difficult substrates such as electron-rich aryl bromides and chlorides. Herein, we report a highly efficient method for the Sonogashira-type cross coupling reaction (Scheme 1) of aryl halides including a few selected activated aryl chlorides using bis(μ-iodo)bis((−)-sparteine)dicopper(I) complex under mild conditions.

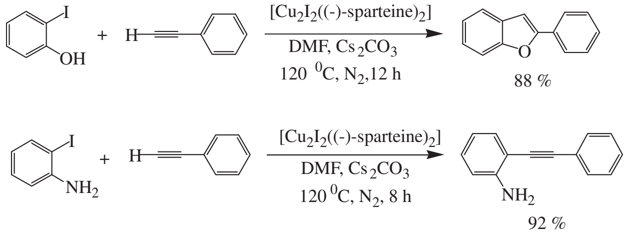
Initially, the coupling reaction between 4-bromoanisole and phenylacetylene was chosen as the model reaction to optimize the reaction conditions. Different copper salts in combination with (−)-sparteine by generating copper complexes in situ, solvents and bases were screened. The results of these studies are summarized in Table 1. As shown in Table 1, different copper(I) salts, such as Cu_2O, CuCl, CuBr and CuI in combination with (−)-sparteine ligand also promote coupling reactions with K_2CO_3 as base in DMSO at 125 °C (Table 1, entries 1–4,). The results show that the choice of copper precursor salts have a profound effect on the reaction as CuBr, CuCl, and Cu_2O afforded only moderate yields of the coupled product [methoxy-4-(phenylethynyl)benzene (Table 1, entries 1–3). When the catalyst was changed to CuI, a good yield of the target product was obtained (entry 4). After screening the bases, it was found that Cs_2CO_3 is the best base for the reaction (entry 5). Then we studied the effect of solvents, such as polar *N*,*N*-dimethylformamide (DMF) and non-polar toluene; *N*,*N*-dimethylformamide proved most efficient for this coupling reaction (entry 7). When pre-formed dimeric bis(μ-iodo)bis((−)-sparteine)dicopper(I) and bis(μ-chloro)bis((−)-parteine)dicopper(I) complexes were evaluated as catalysts (5 mol % relative to the substrate) in DMF for the model reaction, excellent yields for the desired coupled product (Table 1, entry 9 and 10) were obtained.

It can be seen that the reaction with pre-formed catalysts gives much higher yields than that of the in situ system derived from Cu(I) salts and (−)-sparteine.

The optimized reaction conditions[18] were further extended to the reactions of a variety of aryl halides with various phenylacetylenes, using 5 mol % of pre-formed bis(μ-iodo)bis((−)-sparteine)dicopper(I) catalyst, and the results are shown in Table 2. As it can be seen from Table 2, this protocol is rather general in nature for the reactions of electron-rich and electron-deficient haloarenes with phenylacetylenes. The reaction of aryl iodides with phenylacetylene was rather fast, and their coupling reactions gave almost quantitative yields within 4–7 h (Table 2, entries 1 and 3). Usually, aryl bromide substrates require slightly longer reaction times as the reactions of bromobenzene and bromonaphthalene with phenylacetylene took up to 5 h to afford the coupled products in almost quantitative yields (entries 4 and 5). As illustrated in Table 2, electron-rich bromoarenes like *p*-bromoanisole, *p*-bromotoluene, *m*-bromoanisole, *m*-bromotoluene, and *p*-bromothioanisole require even longer reaction times (up to 11 h) to afford the coupled products in >92% yields (entries 6–10). In contrast, reaction of aryl bromide containing an electron-withdrawing group like *p*-NO_2 proceeded much faster to provide an excellent yield for the coupled product (entry 11).

In the hope of broadening the scope of the Sonogashira protocol, we decided to check the efficiency of our catalyst system with less reactive aryl chlorides. As depicted in Table 2, the reactions of phenylacetylene with various aryl chlorides bearing electron-withdrawing groups proceeded smoothly, albeit at slightly longer reaction times (8–12 h). Substrates containing *p*-NO_2, *p*-CN, and *p*-CF_3 and *p*-$COCH_3$ groups gave excellent yields (81–91%) for the corresponding Sonogashira products (entries 12–16). No side products, such as hydrolyzed products were obtained for sensitive functional groups, such as cyano (CN) under our reaction conditions. Notably, chlorobenzene reacts very slowly with phenylacetylene, and even after 24 h of reaction, gave only a poor yield (∼10%) of the coupled product (entry 17). Electron-rich aryl chlorides, such as chlorotoluene and chloroanisole, did not react at all under our reaction conditions. These results are not surprising since most of the copper based catalysts also fail to activate deactivated substrates, such as chlorobenzene and electron-rich chloroarenes for coupling reactions. However, when the reaction of chlorobenzene, chlorotoluene, and chloroanisole were preformed using high catalyst loadings (10 and 20 mol %) poor yields were obtained. (Table 2, entries 17, 21 and 22).

The present catalyst system also works efficiently for sterically hindered aryl halides. For example, *o*-substituted activated *o*-nitrochlorobenzene (entry 16) and aryl iodides (Scheme 2) reacted smoothly with phenylacetylene and furnished excellent yields of the coupled product with slightly longer reaction times (8–12 h) in comparison to their unhindered counterparts. Thus, the reaction of 2-iodoaniline with phenylacetylene gave 2-(phenylethynyl)aniline as the sole product. Uniquely, the reaction of 2-iodophenol with phenylacetylene gave 2-phenylbenzofuran instead of the expected Sonogashira product. The scope of the present protocol was successfully extended to substituted phenylacetylenes, such as 1-ethynyl-4-fluorobenzene and 1-ethynyl-4-methoxybenzene. These substrates also underwent Sonagashira-type coupling and gave good yields of the desired coupled product (Table 2, entries 18–20).



Scheme 2. Reactions of 2-iodophenol and 2-iodoaniline with phenylacetylene.

In conclusion, bis(μ-iodo)bis((−)-sparteine)dicopper(I) is shown to be a versatile catalyst for Sonogashira-type cross coupling reactions of various phenylacetylenes with diverse aryl halides under palladium and phosphine-free reaction conditions. This protocol is also applicable to activated aryl chloride substrates. Since this catalyst is inexpensive and easily synthesizable, this catalytic system should find practical usage for the synthesis of arylacetylenes.

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18. *General procedure*: The reaction vessel was charged with aryl halide (1 mmol), alkyne (1.1 mmol), Cs_2CO_3 (2 equiv) and the catalyst $[Cu_2I_2(spa)_2]$(**1**) (5 mol %) in *N*,*N*-dimethylformamide (3 mL). The reaction mixture was heated at 110–125 °C for the desired time (indicated in Table 2) and the progress of reaction was monitored by TLC. At the end of the reaction, the reaction mixture was cooled to room temperature and was diluted with EtOAc (20 mL), washed with 1 N aq HCl and water. The combined organic phase was dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was subjected to column chromatography on silica gel using ethyl acetate and hexane to afford the desired product in high purity.