

CuBr/*rac*-BINOL-catalyzed Sonogashira reaction of terminal alkynes with aryl halides or arylboronic acids

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Abstract

CuBr/*rac*-BINOL-catalyzed Sonogashira coupling reaction of aryl halides with terminal alkynes was conducted smoothly to afford the corresponding products with moderate to good yields. We found that the inexpensive catalytic system was also suitable for the coupling reaction of arylboronic acids with terminal alkynes.

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Keywords: Sonogashira coupling reaction; Aryl halides; Terminal alkynes; Arylboronic acid; Low cost

1. Introduction

The Sonogashira reaction of terminal alkynes with aryl or vinyl halides has gained great attention in organic synthesis because the molecules containing a carbon–carbon triple-bond moiety are widely used for various functional organic materials, biologically important molecules and their intermediates [1,2]. For example, compounds AGN-193109 and AGN-1943101 (Fig. 1) containing the biaryl alkynes moieties are RAR antagonists for the treatment of mucocutaneous toxicity currently in Phase III clinical trials [3]. Scanning the papers published shows that most commonly used catalytic system for this transformation is a palladium complex combined with a phosphine ligand and CuI [4,5]. However, many phosphine ligands are always expensive and air-sensitive which hampered the applications of the palladium-based catalytic system for the industrial use. Thus, phosphine- and copper-free palladium-catalyzed Sonogashira cross-coupling reactions have been developed [6–10]. In view of the high prices of palladium complexes, chemists aimed at the use of copper (I) alone as the catalyst for the coupling of aryl halides and terminal alkynes [11–14]. In this way, low cost of copper-based catalytic systems makes them particularly

attractive for the potential large-scale industrial applications. However, to our surprise, the few reports relative to the copper-based catalytic systems have been published till now.

Very recently, we have reported our finding about copper-catalyzed C–N cross-coupling reaction at 90–125 °C in the presence of *rac*-BINOL [15]. Separately, Fu et al. found that our protocol could be further optimized to perform the N-arylation coupling reaction at room temperature, which made the cross-coupling reaction more operable [16]. Herein we wish to report the CuBr/*rac*-BINOL-catalyzed Sonogashira reaction of terminal alkynes and aryl halides. In addition, we will show the first example of Sonogashira reaction of terminal alkynes with arylboronic acids using our protocol.

2. Experimental

All reactions were carried out under an argon atmosphere. Solvents were dried and degassed by the standard methods and all halides and alkynes were purchased from Aldrich and Alfa. Flash column chromatography was performed by using silica gel (300–400 mesh). Analytical thin-layer chromatography was performed by using glass plates pre-coated with 200–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). NMR spectra were measured in CDCl₃ on a Varian Inova-400 NMR spectrometer (400 or 300 MHz) with TMS as an internal reference.

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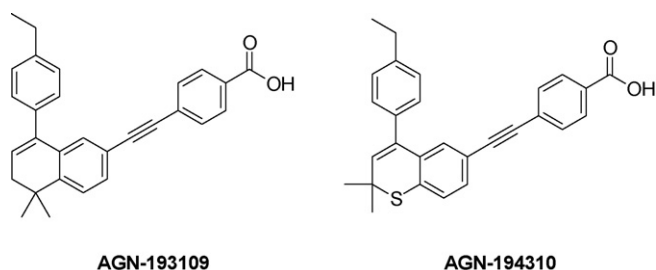


Fig. 1.

2.1. General procedures for Sonogashira reaction of alkynes and halides

A flask was charged with CuBr (14.4 mg, 0.1 mmol), 1,1'-binaphthyl-2,2'-diol (28.5 mg, 0.1 mmol), Cs₂CO₃ (489 mg, 1.5 mmol), and any remaining solids (aryl halide). The flask was evacuated and backfilled with argon (this procedure was repeated three times). Aryl halide (0.5 mmol, if liquid), alkyne (0.6 mmol), and DMF (2 ml) were added to the flask under an argon atmosphere. The flask was sealed and the mixture was allowed to be stirred at the shown temperature for the indicated period of time. After completion of the reaction, the mixture was diluted with ethyl acetate, the solution was filtered and the inorganic salts were removed. The solvent of the filtrate was removed with the aid of a rotary evaporator, and the residue was purified by column chromatography on silica gel, using petroleum ether as eluent to provide the desired product.

2.2. General procedures for Sonogashira reaction of alkynes and arylboronic acids

A flask was charged with CuBr (14.4 mg, 0.1 mmol), 1,1'-binaphthyl-2,2'-diol (28.5 mg, 0.1 mmol), Cs₂CO₃ (489 mg, 1.5 mmol) and arylboronic acids (0.6 mmol). The flask was evacuated and backfilled with argon (this procedure was repeated three times). Alkyne (0.5 mmol) and DMF (2 ml) were added to the flask under an argon atmosphere. Then the same procedure was followed as above.

2.3. Characterization of the representative cross-coupling product

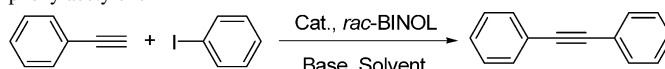
1,2-Diphenylethyne: ¹H NMR (300 MHz, CDCl₃) (δ, ppm): 7.25–7.35 (m, 6H), 7.52–7.54 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) (δ, ppm): 89.84, 128.87, 129.69, 132.09, 132.98.

3. Results and discussions

Initially, we employed the CuBr-catalyzed coupling reaction of iodobenzene with phenylacetylene together with potassium carbonate as the model reaction. Various solvents such as dioxane, THF, toluene, DMF, isopropanol, acetonitrile and DMSO were tested under similar conditions (the temperature was 15 °C) but all gave almost no products except DMF (Table 1, entry 1). When the temperature was elevated to 110 °C, better results

Table 1

Screening conditions for Sonogashira coupling reaction of iodobenzene and phenylacetylene^a



Entry	Cat.	Solvent (T/°C)	Base	Additive	Yield (%) ^b
1	CuBr	DMF (40)	K ₂ CO ₃	–	10
2	CuBr	DMF (70)	K ₂ CO ₃	–	17
3	CuBr	DMF (110)	K ₂ CO ₃	–	37
4	CuBr	DMF (110)	Cs ₂ CO ₃	–	62
5	CuBr	DMF (110)	K ₃ PO ₄ ·nH ₂ O	–	61
6	CuBr	DMF (110)	KO ^t Bu	–	25
7	CuBr	DMF (110)	KF	–	Trace
8	CuBr	DMF (110)	KOH	–	27
9	CuI	DMF (110)	Cs ₂ CO ₃	–	19
10	Cu ₂ O	DMF (110)	Cs ₂ CO ₃	–	2
11	Cu(OAc) ₂ ·H ₂ O	DMF (110)	Cs ₂ CO ₃	–	4
12	Cu	DMF (110)	Cs ₂ CO ₃	–	18
13	CuBr	DMF (110)	Cs ₂ CO ₃	P ^t Bu ₃	3
14	CuBr	DMF (110)	Cs ₂ CO ₃	TBAB	4
15	CuBr	DMF (110)	Cs ₂ CO ₃	CTAB	7
16	CuBr	DMF (110)	Cs ₂ CO ₃	PEG400	21
17	CuBr	PEG 400 (110)	Cs ₂ CO ₃	–	14
18	CuBr	NMP (130)	Cs ₂ CO ₃	–	26
19	–	DMF (130)	Cs ₂ CO ₃	–	Trace
20 ^{c,d}	CuBr	DMF (130)	Cs ₂ CO ₃	–	49
21 ^c	CuBr	DMF (130)	Cs ₂ CO ₃	–	73
22 ^c	CuBr	DMF (130)	K ₃ PO ₄ ·nH ₂ O	–	70
23 ^{c,e}	CuBr	DMF (130)	Cs ₂ CO ₃	–	75

^a Reaction conditions: under an argon atmosphere, phenylacetylene (0.6 mmol), iodobenzene (0.5 mmol), CuBr (0.1 mmol), *rac*-BINOL (0.1 mmol), base (1.5 mmol), solvent, 110 °C, 24 h.

^b Isolated yield based on iodobenzene.

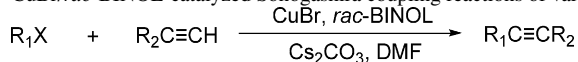
^c Reaction time was 30 h.

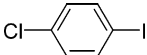
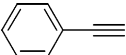
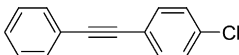
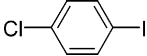
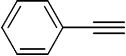
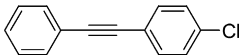
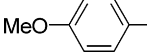
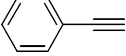
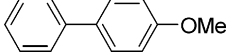
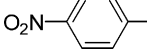
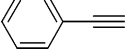
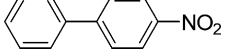
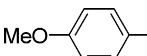
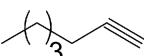
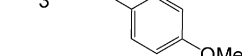
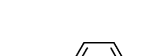

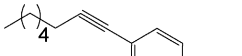
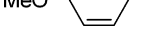
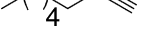

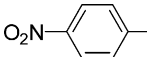
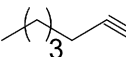
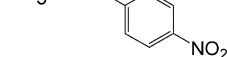
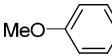
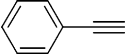
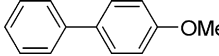
^d No *rac*-BINOL.

^e DABCO instead of *rac*-BINOL.

were obtained for the catalytic reaction performed in DMF (entry 3). Further screening experiments were conducted by using different bases and the best results were got when Cs₂CO₃ and K₃PO₄·nH₂O were employed as the base (entries 4 and 5). Several readily available copper compounds, including CuI, Cu₂O, Cu(OAc)₂·H₂O, and copper powder, were screened for the Sonogashira coupling reaction using Cs₂CO₃ as the base (entries 9–12). The experiments showed that air-stable and inexpensive CuBr gave the best result. We also investigated the coupling reaction with different additives, such as P^tBu₃, TBAB (tetra-*n*-butylammonium bromide), CTAB (cetyl trimethyl ammonium bromide) and PEG-400 (poly(ethylene glycol)), while we did not get more promising results (entries 13–16). By the reuse of the catalytic system, the reaction was conducted in PEG-400 as the solvent to give the yield of 14% (entry 17). NMP (1-methyl-2-pyrrolidine) has always proved to be a good solvent for coupling reactions [17], but we did not obtain any good results using NMP as the solvent even in higher temperature (entry 18). In addition, a series of control experiments was conducted in order to prove the efficiency of our catalytic system. It can be seen that no copper salt gave the corresponding product and no ligand gave moderate yield of the product even under the elevated temperature (130 °C) and longer time (30 h) (Table 1,

Table 2

CuBr/*rac*-BINOL-catalyzed Sonogashira coupling reactions of various halides with alkynes^a

Entry	R ₁ X	R ₂ C≡CH	Product	Yield (%) ^b
1				27
2 ^c				45
3				79
4				87
5				37
6				46
7				37
8				58
9				23

^a Reaction conditions: under an argon atmosphere, phenylacetylene (0.6 mmol), aryl halide (0.5 mmol), CuBr (0.1 mmol), *rac*-BINOL (0.1 mmol), Cs₂CO₃ (1.5 mmol), solvent, 130 °C, 30 h.

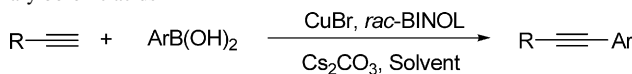
^b Isolated yield based on aryl halide.

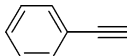
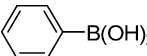
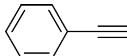
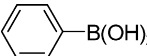
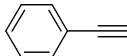
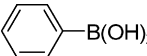
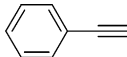
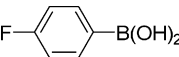
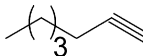
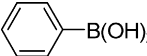
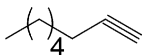
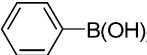
^c K₃PO₄·*n*H₂O used as the base.

entries 19, 20). Thus, 1,2-diphenylethyne was obtained in 73% yield by using the Cs₂CO₃ as the base (entry 21). Under the same conditions, the product was obtained in 70% yield by employing K₃PO₄·*n*H₂O as the base (entry 22). At the same time, the Sonogashira coupling reaction promoted by DABCO (1,4-diazabicyclo[2.2.2]octane) instead of *rac*-BINOL was performed [14], providing a result similar to that of our catalytic system (entry 23).

Based on the above-mentioned optimal conditions, a variety of substrates were examined in the Sonogashira coupling reaction and the results are listed in Table 2. When 1-chloro-4-iodobenzene was used, the coupling products were obtained in yields of 27 and 45% with different bases employed in the catalytic reactions (Table 2, entries 1, 2). To our surprise, either of the halides with electron-donating or electron-withdrawing group on the ring reacting with phenylacetylene gave the good results (entries 3, 4). Especially, from 1-nitro-iodobenzene, we obtained the highest yield of 87% (entry 4). The Sonogashira coupling reaction between aryl iodides with aliphatic alkynes gave poor results (entries 5–7). Therefore, one can conclude that Sonogashira coupling reactions of aromatic alkynes are more favorable than those of aliphatic alkynes. For 4-bromoanisole, the product yield was moderate (58%, entry 8). However, the coupling of bromobenzene with phenylacetylene provided a lower yield (23%, entry 9).

Table 3

CuBr/*rac*-BINOL-catalyzed Sonogashira coupling reactions of alkynes with arylboronic acids^a

Entry	Acetylene	ArB(OH) ₂	Solvent	Yield (%) ^b
1			NMP	6
2			DMF	26
3 ^c			NMP	27
4			DMF	14
5			DMF	16
6			DMF	14

^a Reaction conditions: under an argon atmosphere, alkyne (0.5 mmol), arylboronic acid (0.6 mmol), CuBr (0.1 mmol), *rac*-BINOL (0.1 mmol), Cs₂CO₃ (1.5 mmol), solvent, 130 °C, 30 h.

^b Isolated yield based on alkyne.

^c DABCO as ligand (0.1 mmol).

Table 4
Relationship between the ratio of CuBr with *rac*-BINOL and the catalytic productivity in Sonogashira coupling reaction of iodobenzene and phenylacetylene^a

Entry	Loading of CuBr (mol %)	Loading of <i>rac</i> -BINOL (mol %)	Yield (%) ^b
1	10	10	32
2	10	20	40
3	20	10	11
4	20	20	62
5	20	30	28
6	20	40	84
7	20	50	63
8	40	40	68

^a Under an argon atmosphere: phenylacetylene (0.6 mmol), iodobenzene (0.5 mmol), CuBr (0.1 mmol), *rac*-BINOL (0.1 mmol), Cs₂CO₃ (1.5 mmol), solvent, 110 °C, 24 h.

^b Isolated yield based on iodobenzene.

Although coupling reaction of arylboronic acids and amines has been developed [18–20], coupling reaction of arylboronic acids and alkynes has never been reported till now. In this paper, we will disclose the first example of this type of coupling reactions. The results are summarized in Table 3. The coupling of phenylacetylene with phenyl boronic acid performed in NMP as solvent gave a low yield (Table 3, entry 1). However, DMF instead of NMP provided an enhanced yield of the coupling product (entry 2). Under the same conditions, a better result was obtained when DABCO was used as ligand (27%, entry 3). In addition, the coupling reaction of aliphatic alkynes with phenyl boronic acid did not give good results (entries 4–6). Although the results were not good, it represents an attempt to perform a novel type of Sonogashira reaction.

The dependence of the catalytic productivity on different mole ratios between CuBr and *rac*-BINOL was investigated. The relevant results are listed in Table 4. It can be seen that the ratio between copper salt and ligand is important for the good catalytic productivity and that high loadings of CuBr/*rac*-BINOL is favorable for the catalytic reaction (Table 4, entries 6–8). So we conclude that the ratio between central metal and ligand in the active species is possibly 1:2 (entry 6).

4. Conclusion

In summary, we have developed an efficient, simple, mild and general way to synthesize the biaryl alkynes in moderate to good yields. In comparison with other transition-metal catalyst systems such as the palladium-catalyzed Sonogashira

coupling reaction, this protocol is simple and avoids the use of air-sensitive and expensive catalysts or additives. The easy availability of the catalyst makes this catalytic method useful. In addition, we have also firstly conducted the Sonogashira coupling reaction of alkynes with arylboronic acids, obtaining significant yields. This represents a novel type of Sonogashira coupling reaction. Further studies on highly effective coupling of alkynes with arylboronic acids using novel catalysts are in progress in our laboratory.

Acknowledgments

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