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Catalytic Alkynylation Coupling Reactions by Copper(II) Complex in Water and Its Applications to Domino Synthesis of 2-Arylindoles

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Keywords: Alkynes / Copper / Water chemistry / Domino reactions / Cross-coupling

A mild and clean protocol for the alkynylation coupling of aryl iodides with terminal alkynes has been developed in yields up to 99 % in the presence of sulfonato-Cu^{II}(salen) in water. Domino synthesis of 2-arylindoles from 2-iodoaniline and aryl acetylene was successfully carried out by this catalytic system, and the catalyst could be easily recovered and reused.

Introduction

The transition-metal-catalyzed alkynylation coupling reactions of aryl or alkenyl halides with terminal alkynes is one of the most powerful methods to prepare alkyl–aryl- and diaryl-substituted acetylenes,[1] which are important building blocks for the synthesis of natural products,[2] bioactive molecules,[3] and organic materials.[4] Typical protocols for alkynylation coupling reactions are carried out by a palladium catalyst in conjunction with copper(I) iodide as a co-catalyst under an inert atmosphere in organic solvents such as toluene, DMF, dioxane, or THF.[5] From the standpoint of green chemistry, significant improvements have been obtained by some approaches, including the use of microwave irradiation,[6] ionic liquids,[7] and aqueous media.[6e,8] Obviously, water is one of the most attractive reaction mediums because of its low cost and environmental friendliness,[9] and the most commonly developed catalytic system for this reaction in water involves the use of a palladium complex combined with phosphorus ligands and the recently reported two examples of copper–phosphane catalysts.[6e,8i] However, the sensitivity of phosphorus ligands to air demands that the catalysis be carried out under stringently inert conditions, which greatly restricts its applications. To the best of our knowledge, phosphorus-free, copper-catalyzed alkynylation coupling reactions in water have not yet been reported.[10]

In continuation of our studies in aqueous catalysis of C–N coupling reactions,[9] herein is reported the alkynylation coupling reactions catalyzed by a water-soluble sulfonato–Cu(salen) complex as well as its application to the domino synthesis of 2-arylindoles.

Results and Discussion

Initially, we chose iodobenzene (1 equiv.) and phenylacetylene (1.2 equiv.) as model substrates for the coupling reaction catalyzed by $Cu(OAc)_2$ (10 mol-%) in combination with ligands **L1**–**L5** (10 mol-%) in the presence of K_2CO_3 (1 equiv.) and $(n\mathrm{Bu})_4NBr$ (20 mol-%) at 100 °C for 24 h. As listed in Table 1, when the catalyst was used with ligand **L1** or **L5**, a moderate yield of 64 or 78 %, respectively, was obtained, whereas only a trace amount of the product was found by using **L2**–**L4** (Table 1, Entries 1–5). Isolated pure complex **1** (Figure 1), on the other hand, exhibited preferable catalytic activity in 85 % yield, which was better than the in situ prepared catalyst (Table 1, Entry 6). Screening of different bases suggested NaOH to be the best one, providing the product in ca. 99 % (Table 1, Entry 9), whereas the employment of organic bases such as triethylamine or pyridine resulted in much lower yields (Table 1, Entries 10 and 11). The catalyst loading was then investigated, and it was observed that decreasing the amount of the catalyst resulted in lower yields (Table 1, Entries 12–15). The presence of a phase-transfer catalyst (PTC) was also critical for the catalysis, and no product could be detected without the addition of a surfactant or a phase-transfer reagent (Table 1, Entries 16 and 17). In addition, low temperature decelerated the reaction rate, leading to lower yields (Table 1, Entry 19). Meanwhile, bromobenzene afforded the product in 58 % yield, which was much lower than the iodo analogs (Table 1, Entry 20).

The scope of substrates was then investigated by using this catalytic system under the optimized reaction conditions (10 mol-% of complex **1**, 20 mol-% of PTC, 1.0 equiv. of NaOH). The results are listed in Table 2. In general, most of the substituted aryl iodides afforded the alkynylation products in moderate to good yields ranging from 71 to 94 % (Table 2, Entries 1–8). As expected, aryl iodides with electron-withdrawing groups afforded much higher isolated yields than those with electron-donating groups (Table 2,

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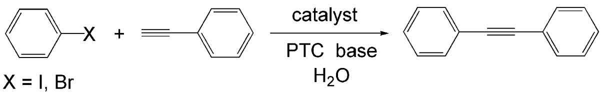
Table 1. Screening reaction conditions for alkynylation coupling reaction of aryl halides with phenylacetylene.[a]



Entry	Catalyst (mol-%)	Base	Yield [%][b]
1	**L1** + $Cu(OAc)_2$ (10)	K_2CO_3	64
2	**L2** + $Cu(OAc)_2$ (10)	K_2CO_3	trace
3	**L3** + $Cu(OAc)_2$ (10)	K_2CO_3	trace
4	**L4** + $Cu(OAc)_2$ (10)	K_2CO_3	trace
5	**L5** + $Cu(OAc)_2$ (10)	K_2CO_3	78
6	**1** (10)	K_2CO_3	85
7	**1** (10)	Cs_2CO_3	72
8	**1** (10)	KOH	98
9	**1** (10)	NaOH	99
10	**1** (10)	Py	14
11	**1** (10)	Et_3N	<10
12	**1** (1)	NaOH	24
13	**1** (2)	NaOH	42
14	**1** (5)	NaOH	79
15	**1** (8)	NaOH	95
16[c]	**1** (10)	NaOH	88
17[d]	**1** (10)	NaOH	94
18[e]	**1** (10)	NaOH	94
19[f]	1 (10)	NaOH	76
20[g]	**1** (10)	NaOH	58

[a] Unless otherwise noted, the reactions were carried out with iodobenzene (1.0 mmol), phenylacetylene (1.2 mmol), catalyst (10 mol-%), PTC (20 mol-%), base (1 mmol) in water (2 mL) at 100 °C. [b] Determined by GC–MS by using 1,4-dichlrobenzene as an internal standard. [c] $(nBu)_4NBr$ (10 mol-%) was added as PTC. [d] $(nBu)_4NBr$ (15 mol-%) was added as PTC. [e] NaOH (0.5 mmol) was added. [f] The reaction temperature was 80 °C. [g] Bromobenzene (1.0 mmol) was used.

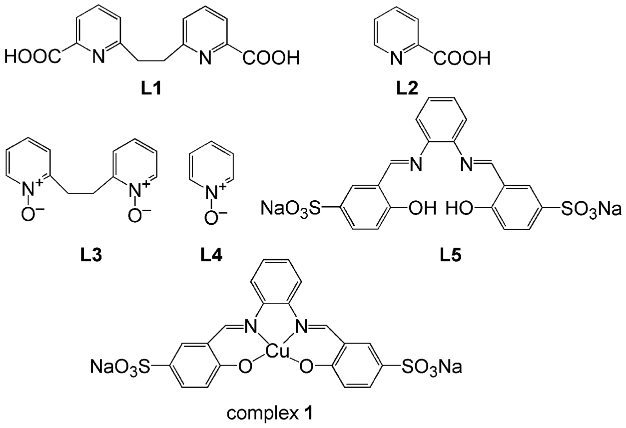
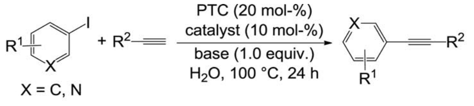
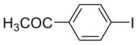
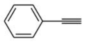
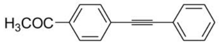
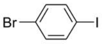
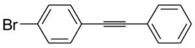
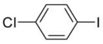
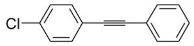
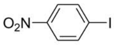
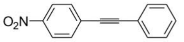
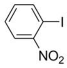
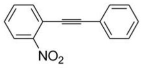
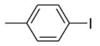
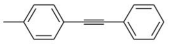
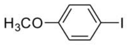
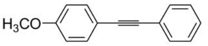
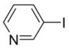
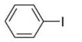
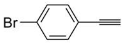
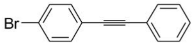
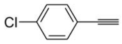
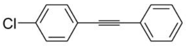
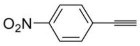
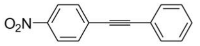
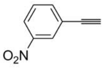
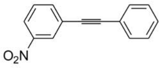
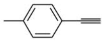
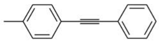
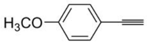
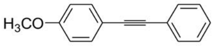
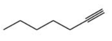
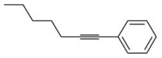


Figure 1. Structure of ligands and complex **1**.

Entries 4 and 6). Due to steric hindrance, *ortho*-substituted aryl iodides gave lower yields than *para*-substituted ones (Table 2, Entries 4 and 5). Furthermore, a heteroaryl iodide could also afford good results when coupling with phenylacetylene (Table 2, Entry 8). In an endeavor to expand the scope of the methodology, this catalytic system was applied to a variety of alkynes. To our delight, most of the substituted alkynes afforded the alkynylation products in yields ranging from 72 to 91% (Table 2, Entries 9–15). In addition, the coupling reaction of an aliphatic alkyne (enanthine) with iodobenzene afforded the product in 78% yield (Table 2, Entry 15).

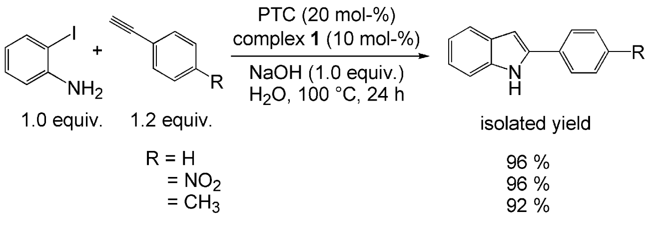
Table 2. The coupling of iodides and different terminal alkynes catalyzed by complex **1**.[a]



Entry	Aryl iodide	Alkyne	Product	Yield [%][b]
1				81
2				93
3				89
4				94
5				88
6				76
7				71
8				89
9				91
10				86
11				91
12				87
13				72
14				82
15				78

[a] Reaction conditions: aryl iodide (1.0 mmol), alkyne (1.2 mmol), catalyst (10 mol-%), NaOH (1 mmol), PTC (20 mol-%), H_2O (2 mL), 100 °C, 24 h. [b] Isolated yield.

On the other hand, indole derivatives widely occur in nature as partial structures of alkaloids and have unique biological activities.[11] Thus, synthetic methods for the preparation of indole derivatives have drawn wide attention.[12] In this case, the catalytic system could be successfully applied in the synthesis of indoles by a cascade process with 2-haloanilines and terminal alkynes. As show in Scheme 1, substituted indoles could be achieved in yields of more than



Scheme 1. Synthesis of 2-arylindoles in water.

90% by using sulfonato–Cu^{II} salen complex as the catalyst under the optimized reaction conditions. The reusability of the catalyst is an important factor in developing an economically and environmentally friendly process. Thus, after the first run in the synthesis of indoles (96% yield) by the cascade process with 2-iodoaniline and phenylacetylene, the product was removed by extraction. The substrates, PTC, and base were then added to the remaining aqueous solution that contained the catalyst for the next run. The recycled catalyst was reused two times and provided the product in yields of 94 and 89%, respectively.

Conclusions

In summary, we have developed a simple, highly efficient, and environmentally friendly protocol for the sulfonato–Cu(salen)-catalyzed alkynylation coupling reaction of aryl iodides with terminal alkynes in water. This method avoids the use of stringent inert conditions. Both alkyl- and aryl-substituted terminal alkynes were found to react efficiently with aryl iodides with good function group compatibility. More importantly, this methodology could be successfully applied to the domino synthesis of 2-arylindoles with 2-haloanilines and terminal alkynes in good yields, which contributed to the first example of utilizing the alkynylation coupling reaction in the synthesis of indoles in water. In addition, the catalyst can be easily recovered and reused.

Experimental Section

Typical Procedure for the Catalysis: Catalyst (0.1 mmol), aryl halide (1.0 mmol), NaOH (1.0 mmol), alkyne (1.2 mmol), (*n*Bu)$_4$NBr (0.2 mmol), and water (2 mL) were added to a sealed tube. The reaction mixture was stirred at 100 °C for 24 h and then cooled to room temperature and extracted with ethyl acetate. The organic layer was then dried with anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The product was finally obtained by column chromatography on silica gel. All the products were confirmed by ^{1}H and ^{13}C NMR spectroscopic analysis.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data, and copies of the ^{1}H and ^{13}C NMR spectra.

Acknowledgments

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