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Copper-catalyzed C(sp²)–C(sp) Sonogashiratype cross-coupling reactions accelerated by polycyclic aromatic hydrocarbons

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Copper-catalyzed Sonogashira-type reactions were dramatically accelerated by introducing a catalytic amount of polycyclic aromatic hydrocarbon additive. This novel catalytic system features low copper loading (0.5 mol% < Cu < 5 mol%), broad reaction scope and remarkable substrate tolerance. Both aromatic and aliphatic terminal alkynes as well as diverse aryl iodides were employed in this transformation, affording respectable yields of the desired products. The novel Cu(OTf)₂/pyrene system was subsequently employed to synthesize phenylacetylene-based fluorescent compounds. Copyright © 2015 John Wiley & Sons, Ltd.

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Keywords: copper catalysis; polycyclic aromatic hydrocarbons; Sonogashira-type cross-coupling reaction

Introduction

Sonogashira coupling reactions are some of the most important methods to furnish arylalkynes or conjugated enynes, which have been used as key precursors for the syntheses of natural products,^[1–3] pharmaceuticals^[4–6] as well as organic materials.^[7,8] Particularly, palladium complexes are the most commonly used catalysts for such transformations, mostly due to their remarkable catalytic efficiency.^[9] Given the fact that palladium is a precious metal with high toxicity, Pd-catalyzed Sonogashira coupling reactions are prohibitively costly. Moreover, expensive phosphine ligands synthesized via tedious multistep processes are usually required to achieve decent reaction efficiency.^[10] Consequently, studies to identify inexpensive and nontoxic alternatives to palladium catalysts are highly desirable. Indeed, it has been found that cost-effective metals like copper can be fairly effective in C-C bond formation reactions, and they seem to function similarly to palladium catalysts in cross-coupling chemistry. Theoretically, copper-catalyzed coupling reactions tend to be more versatile and productive because copper possesses four oxidation states from 0 to +3, whereas palladium species generally have four stable oxidation states of 0, +1, +2 and +4.

It has been known for decades that aryl halides can couple with copper(I) acetylides to afford arylacetylenes.^[11] Recently, it was found that copper(I) catalysts alone can also mediate the coupling reaction of aryl halides and terminal alkynes, such as Cu(I)/amino acid derivatives,^[12–16] Cu(I)/DABCO,^[17] Cu(I)/diamines,^[18–20] copper nanoparticles,^[21–24] supported copper complexes^[25–27] and other copper-based catalytic systems.^[28–32] So far, most Sonogashira coupling reactions are still conducted in the presence of high loadings of copper (5–30 mol%) catalysts and ligands. Therefore, an economic but efficient catalytic system is definitely needed for such C–C bond-forming processes.

Herein, we report the development of an alternative catalytic system for Sonogashira reactions, which utilizes neither phosphine ligands nor palladium catalysts. Specifically, we have discovered that $C(sp^2)-C(sp)$ Sonogashira coupling reactions proceed smoothly in the presence of catalytic amounts of $Cu(OTf)_2$ and polycyclic aromatic hydrocarbons, using potassium carbonate as base and DMF as solvent.

Experimental

General Remarks

All reactions were conducted using a standard Schlenk line. Aryl halides and alkynes were purchased from Aldrich or Alfa Aesar. Cul (99.999%) was purchased from Aldrich. NMR spectra were collected in $CDCl_3$ with a Bruker AVANCE 400 NMR spectrometer (400 MHz) using tetramethylsilane as the internal reference.

Typical Procedure for Cross-Coupling Reactions of Aryl Halides and Terminal Alkynes with Cu/L Catalytic System

A mixture of aryl halide (1.0 mmol), alkyne (1.0 mmol), Cul (4 mol%), ligand **L** (10 mol%) and K_2CO_3 (1 mmol) in DMF (2.5) was stirred for 12 h. The reaction solution was diluted with water, extracted with diethyl ether, dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue obtained was purified using flash column chromatography eluting with hexane or hexane–ethyl acetate.

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Results and Discussion

Using the coupling of iodobenzene and phenylacetylene as a model reaction, the catalytic activity of a diverse set of Cul/L combinations (Cu, 4 mol%; L_1-L_6 (Scheme 1), 10 mol%) was closely examined, affording a 45–96% yield of the desired product (Fig. 1). Specifically, the yield of phenylacetylene was monitored using GC, and then plotted as a function of the reaction time, as illustrated in Fig. 1. To our delight, it appears that ligands L_1-L_6 can accelerate the consumption of starting material to various extents, affording yields ranging from 52 to 90%, which are significantly higher than that observed in the control reaction (37%). In addition, it is found that ligand L_4 is superior to the others, affording a 76% yield of the alkyne product.

Encouraged by these results, we next examined the effect of other reaction parameters. The results are summarized in Table 1. It appears that the catalytic activity of Cul/L is fairly sensitive to the loading of copper catalyst (Table 1, entries 1-9), and those reactions conducted in the presence of 0.5-3 mol% of Cul only afford moderate yield of the desired product (entries 1-4). Surprisingly, when the coupling reaction is carried out in the presence of 4 mol% Cul and 10 mol% L₄, a 94% yield of the desired product is obtained (entry 5). However, further increasing the loading of copper catalyst (up to 30 mol%) does not improve the reaction efficiency; instead, the yield is decreased to 42-45% (entries 6-9). Therefore, the optimal copper loading is 4 mol%. Also, it is known that the concentration of ligand or the ratio of catalyst to ligand might have a substantial impact on catalytic activity.^[26] Therefore, we next investigated the effect of L₄ concentration on the catalytic coupling reaction. As evident from Table 1, a series of Cu-catalyzed cross-coupling reactions were conducted using 4 mol% Cul and 1–30 mol% ligand L_4 (entries 11–18). When the loading of ligand is lower than 10 mol%, the reaction yield is no more than 60%



Scheme 1. Structures of polycyclic aromatic hydrocarbon ligands.



Figure 1. Yield of phenylacetylene.

 Table 1. Cu loading and ligand effect on the cross-coupling reaction of PhI and PhCCH^a

/=\	. ц —	-	Cu, <mark>p</mark>	yrene 10 r	nol%	/=\	
	+ п——		K ₂ CO ₃ , 120 °C, 8 h				
Entry	Cul (mol%)	L 4 (mol%)	Yield (%) ^b	Entry	Cul (mol%)	L₄ (mol%)	Yield (%) ^b
1	0.5	10	38	10	4	0.5	38
2	1	10	41	11	4	1	40
3	2	10	40	12	4	2	43
4	3	10	42	13	4	3	55
5	4	10	93	14	4	4	54
6	5	10	65	15	4	5	63
7	10	10	44	16	4	10	95
8	20	10	39	17	4	20	66
9	30	10	40	18	4	30	40
^a Reaction conditions: iodobenzene (1.0 mmol, 112 μ l), phenylacetylene (1.0 mmol, 109.8 μ l), K ₂ CO ₃ (2.0 mmol, 0.2760 g), DMF (2.5) under nitrogen for 8 h							

(entries 10–15), whereas the reaction yield can reach up to 96% when ligand loading was 10 mol% (entry 16). However, unlike conventional phosphine-based ligands, further increasing the loading of L_4 (10–30 mol%) does not enhance the efficiency

^blsolated yield.

of the coupling reactions (entries 16–18). With the optimal catalytic system in hand, we next investigated the effects of solvent and base. These results are summarized in Table 2. DMF is the most suitable solvent for this transformation, affording a 95% yield of the desired product (Table 2, entry 3). In contrast, solvents such as acetonitrile, toluene and DMSO are found to produce inferior results (entries 1, 2, 4-8). Subsequently, we studied the effects of base on the efficiency of cross-coupling reactions (entries 9-13). As can be seen, K₂CO₃ seems to be the most effective base, with other inorganic bases such as Cs₂CO₃, K₃PO₄, KOt-Bu, KF and KOH producing unsatisfactory results. We also explored the possibility of using organic bases. However, neither of them affords satisfactory results (entries 14 and 15). Finally, we systematically examined the effects of copper sources, in which both Cu(I) and Cu(II) catalysts were employed. Notably, although copper salts such as CuBr, CuCl, CuO and Cu(acac)₂ are also capable of mediating the Sonogashira coupling reaction, only moderate yields (40%) can be obtained, indicating that Cu(OTf)₂ should be the most appropriate copper source (entries 16-21, 20).

We then shifted our efforts to studies of the scope and limitations of this novel catalytic system, using a diverse set of aryl iodides and terminal alkynes (Table 3). Generally, both aryl and aliphatic (1-octyne and 1-hexyne) alkynes can be employed to react with 4-iodoanisole, affording 51–72% yields of the desired products (Table 3, entries 1–4). Specifically, when arylalkynes are allowed to react with aryl iodides, excellent yields of the corresponding products are usually obtained (entries 5–17). However, when *p*-nitroiodobenzene is employed, only a moderate yield of the desired product is isolated (entry 13). It appears that *ortho*-substitution on the aryl iodides proceed smoothly under the standard reaction conditions. Particularly, iodobenzene bearing the strong electron-withdrawing o-CF₃ group reacts very well,

affording 79–92% yields of desired products (entries 9–12). We find that aryl iodides bearing either electron-donating or electronwithdrawing groups can readily react with arylalkynes, affording good to excellent yields of desired products. Notably, the coupling reaction between aryl iodide and aliphatic alkyne gives lower

Table 2 reaction	• Optimization s ^a	of Cu/pyrene-cat	alyzed Sonogasl	hira coupling	
	//	Cu 4 mol%, pyre	ne 10 mol% /		
	+ H-=-("_	K_2CO_3, 120	°C, 8 h		
Entry	Cu	Solvent	Base	Yield (%) ^b	
1	Cul	1,4-Dioxane	K ₂ CO ₃	18	
2	Cul	THF	K ₂ CO ₃	17	
3	Cul	DMF	K ₂ CO ₃	95, 36 ^c	
4	Cul	DME	K ₂ CO ₃	36	
5	Cul	DMSO	K ₂ CO ₃	50	
6	Cul	Toluene	K ₂ CO ₃	46	
7	Cul	Acetonitrile	K ₂ CO ₃	24	
8	Cul	Ethanol	K ₂ CO ₃	20	
9	Cul	DMF	KOH	38	
10	Cul	DMF	Cs ₂ CO ₃	44	
11	Cul	DMF	KF	12	
12	Cul	DMF	K ₃ PO ₄	11	
13	Cul	DMF	KO <i>t</i> -Bu	53	
14	Cul	DMF	Et₃N	25	
15	Cul	DMF	Piperidine	40	
16	CuCl	DMF	K ₂ CO ₃	39	
17	CuBr	DMF	K ₂ CO ₃	40, 41 ^c	
18	CuO	DMF	K ₂ CO ₃	35, 37 ^c	
19	Cu(OAc) ₂	DMF	K ₂ CO ₃	42, 39 ^c	
20	Cu(OTf) ₂	DMF	K ₂ CO ₃	94, 40 ^c	
21	Cu(acac) ₂	DMF	K ₂ CO ₃	40, 38 ^c	

^aReaction conditions: copper salt (4.0 mol%), **L**₄ (0.1 mmol, 0.0016 g), base (2 mmol), aryl iodide (1 mmol, 112 μ l) and alkyne (1 mmol, 109.8 μ l) in 2.5 ml solvent were stirred for 8 h under nitrogen. ^bIsolated yield. ^cNo additives. yields (50%, entry 18). Finally, the coupling reactions using bromobenzene and chlorobenzene with phenylacetylene under the optimal reaction conditions turn out to give low yields of 24% and less than 5%, respectively.

Based on the well-established mechanism reported by Miura and co-workers,^[11] Rothenberg and co-workers^[24] and Li and coworkers^[33] (Scheme 2), we propose a plausible mechanism for the Cu(OTf)₂/pyrene-catalyzed Sonogashira cross-coupling reaction. At first, **L** coordinates with Cu(OTf)₂ to generate a transition state intermediate **I**, as proposed by Stephens and Castro.^[34] Subsequently, complex **I** reacts with alkyne to afford intermediate **II** in the presence of potassium carbonate, followed by oxidative addition reaction with PhI to give intermediate **IV**. Finally, **IV** undergoes reductive elimination to afford the desired coupling product, accompanied by the regeneration of the active copper species **I**. In the meantime, homocouplings of terminal alkynes proceeding through the intermediacy of **II** can give diyne byproduct **V**.^[35–38] Further investigations to understand the mechanistic role of ligand **L** are currently in progress.

Because we are interested in the development of novel fluorescent dyes, nonlinear optical materials and photorefractive materials^[39,40] with strong π - π conjugation, we hope to utilize the



 $\ensuremath{\mathsf{Scheme}}$ 2. Proposed mechanism of Cu/L-catalyzed Sonogahria cross-coupling.

Table 3. Cul/pyrene-catalyzed Sonogashira cross-coupling of aryl iodides and terminal alkynes ^a								
$R_1 + H - R_2 \xrightarrow{\text{pyrene, 10 mol\%}} R_2 \xrightarrow{\text{pyrene, 10 mol\%}} R_2$								
Entry	R ₁	R ₂	Yield (%) ^b	Entry	R ₁	R ₂	Yield (%) ^b	
1	<i>p</i> -MeO	Ph	68	10	o-CF ₃	p-MeC ₆ H ₄	86	
2	<i>p</i> -MeO	p-MeC ₆ H ₄	72	11	o-CF ₃	<i>p</i> -EthylC ₆ H ₄	79	
3	<i>p</i> -MeO	<i>n</i> -Pentyl	51	12	o-CF ₃	<i>p</i> -PentylC ₆ H ₄	85	
4	<i>p</i> -MeO	<i>n</i> -Ethyl	55	13	p-NO ₂	p-MeC ₆ H ₄	70	
5	m-CH ₃	Ph	77	14	Н	Ph	96	
6	m-CH ₃	p-MeC ₆ H ₄	89	15	Н	p-MeC ₆ H ₄	88	
7	<i>m</i> -CH₃	p-EthylC ₆ H ₄	84	16	Н	<i>p</i> -EthylC ₆ H ₄	90	
8	m-CH ₃	<i>p</i> -PentylC ₆ H ₄	79	17	Н	<i>p</i> -PentylC ₆ H ₄	82	
9	o-CF ₃	Ph	92	18	m-CH ₃	<i>n</i> -Pentyl	50	

^aReaction conditions: Cu(OTf)₂ (4 mol%), pyrene (0.1 mmol, 0.0016 g), K₂CO₃ (2 mmol, 0.2760 g), aryl iodide (1 mmol), alkyne (1 mmol), in DMF (2.5), for 16 h. ^bIsolated yield.

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Scheme 3. Coupling reaction between diiodobenzene/dibromobenzene and phenylacetylene.

coupling reaction of phenylacetylene and 1,2-diiodobenzene or 1,3-diiodobenzene to furnish such molecules. Indeed, the coupling reactions of aryl diiodides with phenylacetylene were carried out using the standard Cu(OTf)₂/L₄ catalytic system, affording an excellent yield of the diyne products, as shown in Scheme 3. Both diiodobenzene and dibromobenzene were subject to the standard coupling conditions, and the former seems to be more active for the cross-coupling reaction. Notably, mono- and di-substituted substrates are formed non-selectively by the coupling reaction of 1,3-diiodobenzene (1 equiv.) and phenylacetylene (1.5 equiv.). It is found that increasing the amount of phenylacetylene (2.0 equiv.) can lead to higher yield of bi-substituted product $(\mathbf{a}_1, \mathbf{a}_3, \mathbf{a}_5 \text{ and } \mathbf{a}_7)$. The double cross-coupling reaction of 1,3-diiodobenzene (1 equiv.) and phenylacetylene (2.0 equiv.) affords **a**₃ with 84% yield, along with mono-substituted product \mathbf{a}_4 in 11% yield. Therefore, we conclude that the best results can only be obtained using the optimal ratio of alkyne to diiodobenzene.

Conclusions

A highly effective catalytic system using Cu(OTf)₂ catalyst and polycyclic aromatic hydrocarbon ligand L₄ (pyrene) has been developed for Sonogashira-type cross-coupling reactions. This novel combination features broad reaction scope and remarkable substrate tolerance, affording moderate to excellent yields of the desired products. In addition, this catalytic system is fairly affordable for both industrial and academic settings, since its cost is about one-tenth of

that of similar catalyst systems.^[41] Finally, several fluorescent diynes have been prepared using the protocol developed in our laboratory.

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