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The Copper-Catalyzed Cross-Coupling Reactions of Aryl Diazonium Salts and Isocyanides[1]

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Abstract—The copper-catalyzed cross-coupling reaction of aryl diazonium salts and isocyanides has been performed. This is a successful example of preparation of arylcarboxyamides with moderate to good yield under mild conditions.

Keywords: copper, coupling, isocyanide, aryl diazonium salt

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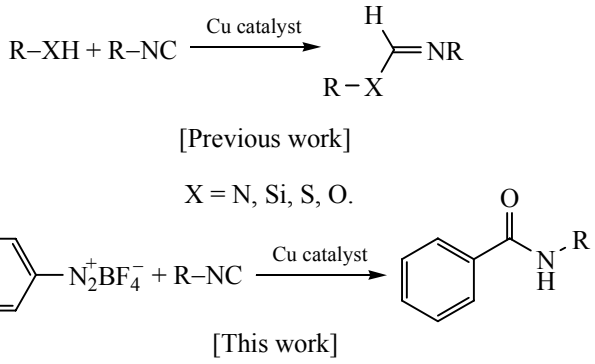
Palladium-catalyzed isocyanides transformations have been intensively studied over the recent two decades [1–5]; the reaction serving as a convenient approach to prepare a variety of heterocyclic compounds containing nitrogen atom [6–10]. For example, the palladium-catalyzed carbonylation reaction has drawn considerable interest [11–17]. In 2012, Zhu and Ji reported a nice method for the synthesis of isocoumarins and phthalides via the palladium-catalyzed coupling incorporating *tert*-butyl isocyanide, providing a simple method for the synthesis of valuable lactones [18]. Later, Jiang et al. reported a palladium-catalyzed and CsF-promoted annulation reaction of bromoalkynes and isocyanides. That process provided an efficient method to obtain a diverse set of 5-iminopyrrolone derivatives [19]. In 2013, Kaim, Gamez-Montano, and Grimaud reported a new procedure for arylation of isocyanides with diazonium salts, showing a new fashion of aryl nitrilium species coupling with isocyanides as a key intermediate [20]. In 2013, Lang and co-workers demonstrated a convenient palladium-catalyzed cascade process for the preparation of both benzoxazoles and benzothiazoles with isocyanides as starting materials [21]. Recently, Zhu and co-workers developed an efficient palladium-catalyzed cyanation by using tertiary amine-derived isocyanide as a novel cyano source [22]. Later, they showed a convenient arylation of isocyanides through aryl radical intermediates with good yields. That reaction provided a formal aminocarbonylation reaction using aryl diazonium salts as electrophiles [23].

Compared with palladium-catalyzed isocyanide reactions [24–29], the copper-catalyzed isocyanide transformations are relatively slow. It has been found that copper catalyst would promote the isocyanide insertion into N–H, Si–H, S–H, and O–H bonds [30]. The coordination of isocyanide compound and copper catalyst occurs to give the copper adduct containing the isocyanide-compound, followed by the addition to afford the finally products [2]. Herein, we report on the copper-catalyzed cross-coupling reactions of aryl diazonium salts and isocyanides (Scheme 1). The reaction provided a convenient method to prepare arylcarboxyamides with moderate to good yields under mild reaction conditions.

We started the experiment with phenyl diazonium salt and *tert*-butyl isocyanide as the model substrates. The reaction of phenyl diazonium salt and *tert*-butyl isocyanide was set up with CuCl as a catalyst. To our pleasure, the desired product was obtained with 26% yield. A series of screening reaction conditions were trialed in order to enhance the product yield. The

[1] The text was submitted by the authors in English.

Scheme 1. Cu-catalyzed isocyanide insertion reactions.



experiments on catalyst variation revealed that CuI produced the highest product yield (Table 1, entries 1–5). Variation of the solvent showed that *N*,*N*-dimethylformamide (DMF) gave the best reaction outcome (Table 1, entries 6–10). Finally, the effect of the base was also screened. The similar yields were obtained with several common bases used in the reaction (Table 1, entries 11–15). The best reaction conditions were as follows: DMF as the solvent, potassium carbonate as the base, and CuCl as the catalyst (Table 1, entry 11).

With the best reaction conditions in hand, we explored the reaction scope of aryl diazonium salts and isocyanides. In most cases, the desired products were obtained with moderate to good yields. The much higher yields were achieved when an electron-withdrawing group was present in aryl diazonium salts

Scheme 2. The proposed reaction mechanism for the reaction of aryl diazonium salts and isocyanides.

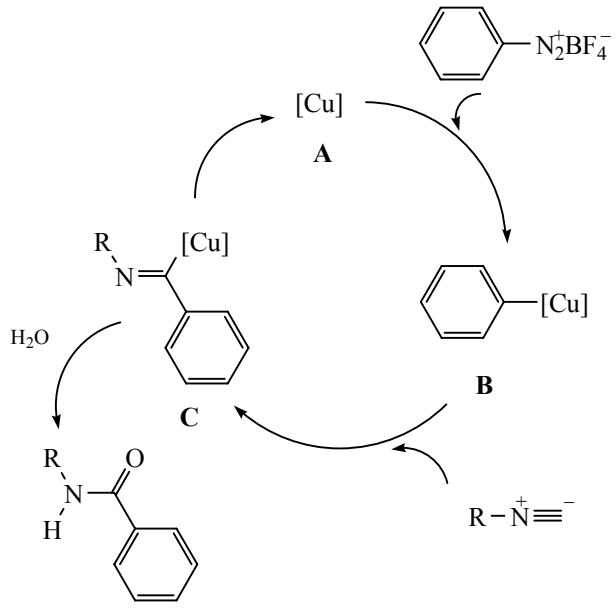
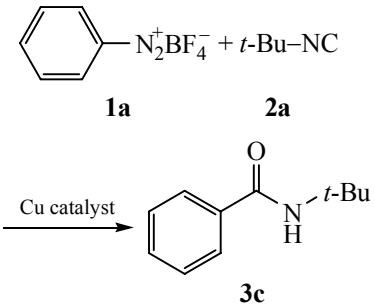


Table 1. Copper-catalyzed carbonylative coupling of phenyl diazonium salt[a]



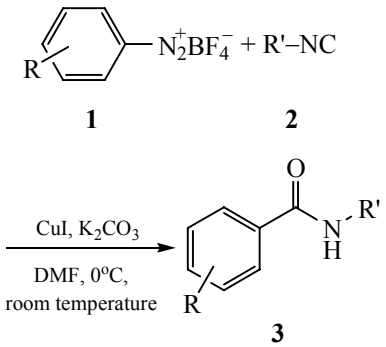
Entry	Catalyst	Solvent	Base	Yield, %[b]
1	CuCl	DMF	Na_2CO_3	26
2	CuBr	DMF	Na_2CO_3	32
3	CuI	DMF	Na_2CO_3	35
4	$Cu(OAc)_2$	DMF	Na_2CO_3	18
5	$FeCl_3$	DMF	Na_2CO_3	<5
6	CuI	Toluene	Na_2CO_3	<5
7	CuI	CH_3CN	Na_2CO_3	21
8	CuI	DCM	Na_2CO_3	<5
9	CuI	THF	Na_2CO_3	<5
10	CuI	DMSO	Na_2CO_3	30
11	CuI	DMF	K_2CO_3	46
12	CuI	DMF	Cs_2CO_3	42
13	CuI	DMF	NaOAc	34
14	CuI	DMF	K_3PO_4	27
15	CuI	DMF	–	11

[a] Conditions: **1a** (0.6 mmol, 1.0 equiv.), **2a** (2.4 mmol), catalyst (0.1 mol %), H_2O (5 equiv.), 3 mL solvent, 2 h, 0°C–rt. [b] Isolated yields base on **1a**.

(Table 2, entries 6, 8, and 12). The electron-rich substrates gave the desired products with substantially lower yield. The meta-substituted aryl diazonium tetrafluoroborates also reacted with isocyanides smoothly affording the good yields (Table 2, entries 5 and 8).

Finally, the possible mechanism was also proposed. According to the literature [31–33], the first step of the cycle was likely the formation of aryl-Cu species (**B**) from the diazonium salt and the copper catalyst [31]. After the coordinative insertion of the isocyanides, the intermediate (**C**) was formed, further reacting with water to afford the target product (Scheme 2).

Table 2. Copper-catalyzed carbonylative couplings of aryl diazonium salt[a]



Entry	R	R'	Yield, %[b]	Product
1	H	*t*-Bu	46	**3a**
2	*p*-Me	*t*-Bu	51	**3b**
3	*p*-MeO	*t*-Bu	42	**3c**
4	*p*-Cl	*t*-Bu	53	**3d**
5	*m*-Cl	*t*-Bu	56	**3e**
6	*p*-NO_2	*t*-Bu	76	**3f**
7	*p*-CF_3	*t*-Bu	63	**3g**
8	*m*-NO_2	*t*-Bu	71	**3h**
9	*p*-Cl	*i*-Pr	48	**3i**
10	*p*-Cl	Cyclohexyl	62	**3j**
11	*p*-NO_2	*i*-Pr	54	**3k**
12	*p*-NO_2	Cyclohexyl	70	**3l**

[a] Conditions: **1a** (0.6 mmol, 1.0 equiv.), **2a** (2.4 mmol), CuI (0.1 mol %), H_2O (5 equiv.), 3 mL DMF, 2 h, 0°C–room temperature. [b] Isolated yields base on **1a**.

In conclusion, we have developed an efficient copper-catalyzed cross-coupling reaction of aryl diazonium salts and isocyanides. This is a successful example to synthesis of arylcarboxyamides with moderate to good yield under mild reaction conditions.

EXPERIMENTAL

All the solvents were used without purification. The products were isolated by column chromatography on silica gel (200–300 mesh) using ethyl acetate and hexane as the eluents. The reaction progress was monitored by TLC developing with UV light. ^{1}H NMR chemical shifts were referenced to TMS. The spectra were recorded using $CDCl_3$ as a solvent.

Aryl diazonium tetrafluoroborates *(general procedure).* The corresponding aniline (5 mmol) was added to a mixture of distilled water (3 mL) and 50% hydrofluoroboric acid (1.8 mL). After cooling the reaction mixture to 0°C, the solution of sodium nitrite (0.35 g in 1 mL of water) was added over 10 min, and the reaction mixture was stirred during 45 min at 0°C. The solid product was collected by filtration and re-dissolved in several drops of acetone. Next, diethyl ether was added to the solution of diazonium tetrafluoroborate in acetone, the precipitate was filtered off again, washed with ether several times, and dried.

Arylcarboxyamides *(general procedure).* Isocyanide (4 equiv.) was added to a solution of diazonium tetrafluoroborate in DMF at 0°C using a Schlenk tube, under nitrogen atmosphere. The catalyst and potassium carbonate were added at 0°C. Water (5.0 equiv.) was then added. The mixture was stirred at 0°C during 1 h and then at room temperature during 1 h. After the reaction was complete, ethyl acetate (10 mL) and water (10 mL) were added to the reaction mixture. After separation, the water layer was washed by ethyl acetate (2 × 10 mL). The organic layers were combined; the mixture was concentrated under reduced pressure and purified by column chromatography.

***N*-(*tert*-Butyl)benzamide (3a).** ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 7.75 d (*J* = 7.0 Hz, 2H), 7.49 t (*J* = 7.8 Hz, 1H), 7.43–7.40 m (2H), 5.94 s (1H), 1.47 s (9H).

***N*-(*tert*-Butyl)-4-methylbenzamide (3b).** ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 7.64 d (*J* = 8.4 Hz, 2H), 7.23 d (*J* = 8.4 Hz, 2H), 5.93 s (1H), 2.41 s (3H), 1.48 s (9H).

***N*-(*tert*-Butyl)-4-methoxybenzamide (3c).** ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 7.71 d (*J* = 8.6 Hz, 2H), 6.93 d (*J* = 8.7 Hz, 2H), 5.89 s (1H), 3.85 s (3H), 1.48 s (9H).

***N*-(*tert*-Butyl)-4-chlorobenzamide (3d).** ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 7.68 d (*J* = 8.4 Hz, 2H), 7.41 d (*J* = 8.4 Hz, 2H), 5.81 s (1H), 1.49 s (9H).

***N*-(*tert*-Butyl)-3-chlorobenzamide (3e).** ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 7.71 s (1H), 7.59 d (*J* = 7.8 Hz, 1H), 7.45 d (*J* = 8.2 Hz, 1H), 7.38–7.33 m (1H), 5.93 s (1H), 1.47 s (9H).

***N*-(*tert*-Butyl)-4-nitrobenzamide (3f).** ^{1}H NMR spectrum (400 MHz, $CDCl_3$) 8.26 d (*J* = 8.6 Hz, 2H), 7.88 d (*J* = 8.6 Hz, 2H), 6.05 s (1H), 1.49 s (9H).

***N*-(*tert*-Butyl)-2-iodo-4-(trifluoromethyl)benzamide (3g).** ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 8.09 s (1H), 7.66–7.61 m (1H), 7.49 d (J = 8.2 Hz, 1H), 5.54 s (1H), 1.50 s (9H).

***N*-(*tert*-Butyl)-3-nitrobenzamide (3h).** ^{1}H NMR spectrum (400 MHz, $CDCl_3$) 8.53–8.50 m (1H), 8.31–8.26 m (1H), 8.10 d (J = 7.8 Hz, 1H), 7.60 t (J = 8.2 Hz, 1H), 6.23 s (1H), 1.50 s (9H).

***N*-Isopropyl-4-chlorobenzamide (3i).** ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 7.71 d (J = 8.4 Hz, 2H), 7.40 d (J = 8.4 Hz, 2H), 6.03 s (1H), 4.29–4.25 m (1H), 1.27 d (J = 6.6 Hz, 6H).

***N*-Cyclohexyl-4-chlorobenzamide (3j).** ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 7.71 d (J = 8.6 Hz, 2H), 7.40 d (J = 8.6 Hz, 2H), 6.05 s (1H), 3.97 m (1H), 2.04–1.19 m (10H).

***N*-Isopropyl-4-nitrobenzamide (3k).** ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 8.30 d (J = 8.6 Hz, 2H), 7.93 d (J = 8.6 Hz, 2H), 6.01 s (1H), 4.35–4.31 m (1H), 1.30 d (J = 7.0 Hz, 6H).

***N*-Cyclohexyl-4-nitrobenzamide (3l).** ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 8.29 d (J = 8.8 Hz, 2H), 7.94 d (J = 8.8 Hz, 2H), 6.05 s (1H), 3.99 m (1H), 2.08–1.23 m (10H).

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