A Highly Versatile Catalytic System for *N*-Arylation of Amines with Aryl Chlorides in Water

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The C–N coupling between nucleophiles and aryl chlorides, which are less expensive, less reactive, and more abundant than their bromide and iodide counterparts, is challenging but of great interest for industrial applications. An oxalyldi-

Introduction

Many significant products (drugs, materials, optical devices, etc.), whether commercialized or at the development phase, possess aromatic carbon-nitrogen bonds.^[1] Until now, Pd-^[1a,2] and Cu-catalyzed^[2j,3] cross-coupling reactions have been the most efficient for the construction of aromatic C-N bonds both in industrial and academic settings, although traditional Cu-mediated C-N cross-couplings, such as the Ullmann and Goldberg-type reactions, have showed limitations in practical applications due to the requirement of stoichiometric amounts of copper reagents and harsh reaction conditions. The study of copper-catalyzed C-N couplings has been reinvigorated because of the potential attractiveness of copper and Buchwald's and Taillefer's pioneering work^[3a,4] followed by others.^[3e,5] The latter judiciously employed selected ligands enabling the coupling to be performed under mild conditions with a catalytic amount of copper.

From general considerations, aryl chlorides are less expensive and more abundant than their bromide and iodide counterparts, but they less reactive and of much greater interest for industrial applications. However, the development of several highly effective classes of catalysts for the cross-coupling of aryl chlorides with low catalyst loadings, excellent yields, and reasonable scope remains a challenging.^[2a,6] It has rarely been mentioned in the literature that Cu-catalyzed C–N coupling reactions of aryl chlorides with arylamines are difficult: For example, cyclohexane-1,2-diamine as a ligand facilitates the CuI-catalyzed amination of aryl chlorides when performed with an excess amount of

hydrazide/hexane-2,5-dione (100-150 mol-%)/CuO system was found to enable the reaction of a wide range of nucleophiles with a variety of aryl chlorides in water for the first time.

the aryl chloride as the solvent (51–95% isolated yields);^[4a] with the assistance of microwave heating (10-20 h), aryl chlorides have been successfully aminated with aqueous ammonia by using a Cu₂O-catalyzed system in water/NMP (1:1).^[7] However, additional studies are strongly needed to develop a versatile copper catalytic system that can couple a broad spectrum of potential amines with aryl chlorides under mild conditions. Furthermore, protocols avoiding the use of toxic and/or high-boiling organic solvents have recently attracted much attention to fulfill one or more requirements of a sustainable chemistry. Hence, Ullmanntype C-N reactions of aryl bromides and aryl iodides have successfully been performed in pure water or aqueous media.^[2h,5g,8] As part of our ongoing research interest in aqueous organic reactions,^[8a-8c,8f] we report herein an oxalyldihydrazide/hexane-2,5-dione/CuO system for the amination of aryl chlorides in water that does not requiring an inert atmosphere or microwave irradiation.

Results and Discussion

Previously, we described an oxalyldihydrazide/ketone/ CuO system that enabled the amination of aryl halides in water. In particular, some aryl chlorides were aminated to afford trace amounts of the desired products.^[8a] Hence, it is reasonable to develop a versatile catalytic system for the *N*-arylation of amines with aryl chlorides in water by extending the reaction time from minutes to hours. To test this hypothesis, we used the previously described conditions for the reaction between 4-bromoanisole and aniline for the amination of 4-chloroanisole. Thus, we found that 4-chloroanisole afforded 4-methoxy-*N*-phenylaniline in 14% isolated yield upon heating for 8 h in a preheated oil bath (Scheme 1).



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Scheme 1. Model reaction for the amination of aryl chlorides.

This promising result encouraged us to screen typical reaction parameters including different copper sources, bases, ketones as well as different proportions of substrates, catalysts, and ligands. A range of different copper sources (Cu^{II} and Cu^I) were more or less active, but CuO provided the highest yields (Table 1). The latter has the advantage of being inexpensive and air stable. However, the amount of CuO was much more important to make full conversion (10 mol-%). The choice of base and ketone was another important factor. K₃PO₄ was found to be the best base, affording excellent conversion and yield (98% conversion, 82% GC yield), although Cs₂CO₃ and K₂CO₃ also provided high conversion. However, KOH (a strong base) afforded a much lower conversion and a poor yield. This disparity probably results from the need to match the rate of deprotonation of the amine to the rate of C-N bond formation.^[3a] With regard to the ketone, we found that hexane-2,5-dione was a prerequisite for obtaining high activity (98% conversion and 82% GC yield), and other related ketones afforded much lower conversions and poor yields (data not presented here). After a brief optimization campaign, it was discovered that employing oxalyldihydrazide/hexane-2,5-dione/ CuO (50:100:10 mol-%) at 120 °C in water gave 98% conversion of 4-chloroanisole into 4-methoxy-N-phenylaniline with 73% isolated yield after 24 h (Scheme 2, 3a). Thus, we obtained the first effective example for the Cu-catalyzed coupling of nonactivated aryl chlorides in water with no microwave irradiation. It should be noted that oxalylhydrazide is crucial for the effective copper-catalyzed C-N coupling in water, although its role is not yet well understood (Table 1, Entry 19).

In most cases, *N*-arylation of aniline with most aryl chlorides (electron-rich, electron-neutral, or electron-poor) provided the desired products in good isolated yields. As for *ortho*-substituted aryl chlorides, the reaction was slower and less efficient and afforded the corresponding 2-methoxy-*N*phenylaniline (Scheme 2, **3d**) in only 37% isolated yield after 24 h. This observation was relevant to Cu-catalyzed systems because of steric hindrance.^[9]

Notably, a much larger excess of benzylamine (6 equiv.) and hexane-2,5-dione (1.5 equiv.) were needed to provide complete conversion of the aryl chlorides due to unexpected Paal–Knorr side reactions^[8a] that consumed the benzylamine and hexane-2,5-dione, reducing the yield of the desired products.

It is very interesting to apply the procedure for the preparation of anilines, which are key intermediates in aromatic processes.^[10] Microwave-assisted direct amination of aryl chlorides with ammonia has been reported.^[7] In most cases (Scheme 3, **3m**, **3n**, **3o**, **3p**), the corresponding anilines were Table 1. Optimization of coupling reaction of 4-chloroanisole with aniline $^{\left[a\right] }$

CI +		[Cu] oxalyldihydrazide hexane-2,5-dione		H
0 Pro, base, 2 mil H ₂ O V O 120 °C, 24 h				
Entry	[Cu] (mol-%)	Base (mol-%)	PTC (mol-%)	Conv. / Yield $(\%)^{[b]}$
1	none	$K_{3}PO_{4}(2)$	TBAB (25)	0/0
2	CuO (10)	$K_{3}PO_{4}(2)$	TBAB (25)	98/82
3	CuO (1)	$K_{3}PO_{4}(2)$	TBAB (25)	54/44
4	CuO (5)	$K_{3}PO_{4}(2)$	TBAB (25)	96/73
5	CuI (10)	$K_{3}PO_{4}(2)$	TBAB (25)	58/30
6	$Cu_2O(10)$	$K_{3}PO_{4}(2)$	TBAB (25)	26/22
7	CuCl (10)	$K_{3}PO_{4}(2)$	TBAB (25)	98/76
8	Cu (10)	$K_{3}PO_{4}(2)$	TBAB (25)	20/17
9	CuSO ₄ (10)	$K_{3}PO_{4}(2)$	TBAB (25)	21/13
10	CuO (10)	$K_{3}PO_{4}(1.5)$	TBAB (25)	97/73
11	CuO (10)	$K_{3}PO_{4}(3)$	TBAB (25)	90/70
12	CuO (10)	KOH (2)	TBAB (25)	31/24
13	CuO (10)	$Cs_2CO_3(2)$	TBAB (25)	98/77
14	CuO (10)	$K_2CO_3(2)$	TBAB (25)	100/79
15	CuO (10)	$K_{3}PO_{4}(2)$	none	12/10
16	CuO (10)	$K_{3}PO_{4}(2)$	SDS-Na (25)	66/56
17	CuO (10)	$K_{3}PO_{4}(2)$	TBAB (10)	83/70
18	CuO (10)	$K_{3}PO_{4}(2)$	TBAB (50)	94/74
19	CuO (10)	$K_{3}PO_{4}(2)$	TBAB (25)	0/0 ^[c]
20	CuO (10)	$K_{3}PO_{4}(2)$	TBAB (25)	52/40 ^[d]
21	CuO (10)	$K_{3}PO_{4}(2)$	TBAB (25)	89/66 ^[e]
22	CuO (10)	$K_{3}PO_{4}(2)$	TBAB (25)	94/69 ^[f]
23	CuO (10)	$K_{3}PO_{4}(2)$	TBAB (25)	92/73 ^[g]
24	CuO (10)	$K_{3}PO_{4}(2)$	TBAB (25)	0/0 ^[h]
25	CuO (10)	$K_{3}PO_{4}(2)$	TBAB (25)	32/24 ^[i]
25	CuO (10)	$K_{3}PO_{4}(2)$	TBAB (25)	96/79 ^[j]

[a] Reaction conditions: 4-chloroanisole (1.0 mmol), aniline (4.0 mmol), catalyst, oxalyldihydrazide (25 mol-%), hexane-2,5-dione (100 mol-%), base, phase-transfer catalyst (PTC), H_2O (2.0 mL), 120 °C, 24 h. [b] Calculated GC yield. [c] No oxalyldihydrazide was used. [d] Oxalyldihydrazide (10 mol-%). [e] Oxalyldihydrazide (20 mol-%). [f] Aniline (2.0 mmol). [g] Aniline (3.0 mmol). [h] No hexane-2,5-dione was used. [i] Hexane-2,5-dione (50 mol-%). [j] Hexane-2,5-dione (200 mol-%).

obtained in good yields (72–80%) without the use of strong bases, toxic and expensive metals, or sophisticated ligands.

Azoles and arylazoles play an important role as structural and functional units in many biologically active compounds, natural products, and useful synthons. However, the preparation of *N*-arylazoles is severely restricted, because nitrogen heterocycles are not good substrates for the traditional arylation reagents.^[11] We were pleased to find that the arylation reaction also proceeds with pyrazole in good to excellent yields when extending the reaction time to 48 h. However, the reaction between imidazole or 1*H*benzimidazole and aryl chlorides afforded fair to good yields of the corresponding products due to incomplete conversion of aryl chlorides.

It should be noted that nitro-substituted aromatic chlorides were not good substrates for amination under the experimental conditions. Although the desired cross coupling products were still obtained in fair yields (Scheme 2, **3e**, **3k**;



Scheme 2. Products and yields for Cu-catalyzed amination of aryl chloride with different nitrogen sources.

Scheme 3, **3p**, **4d**, **4m**) in most cases, pyrazole coupling to 1-chloro-4-nitrobenzene afforded 4-(1H-pyrazol-1-yl)aniline as the main product (70% isolated yield), which was formed during the reduction of the nitro group by the CuO/ oxalyldihydrazide system.

Conclusions

In conclusion, we have reported a versatile protocol for the CuO-catalyzed amination of aryl chlorides in water. It obviates the need for microwave irradiation, has a broad substrate scope, which includes various nitrogen sources ranging from arylamines to nitrogen-containing aromatic heterocycles, and includes a range of aryl chlorides (both activated and unactivated ones). Considering the large variety and ready availability of the starting materials, as well as the stability and low price of CuO, in addition to the operational simplicity of our procedure, a convenient, practical, and highly efficient catalytic system for C–N crosscoupling of aryl chlorides was developed for the first time. Further investigations to understand the mechanism concerning the origin of the broad scope and high activity of the catalysts featured herein are currently ongoing in our laboratory.

Experimental Section

Representative Procedure: A 10-mL vessel was charged with CuO (10 mg, 0.1 mmol), oxalyldihydrazide (59 mg, 0.5 mmol), hexane-2,5-dione (114 mg, 1.0 mmol), aryl chloride (1.0 mmol), amine (4.0 mmol), K₃PO₄·3H₂O (532 mg, 2.0 mmol), TBAB (80 mg, 0.25 mmol), H₂O (2.0 mL) and a magnetic stir bar. The vessel was sealed with a septum and placed into an oil bath, which was preheated to 120 °C. The reaction mixture was held at this temperature for 24 h. After allowing the mixture to cool to room temperature, the reaction mixture was extracted with ethyl acetate $(4 \times 30 \text{ mL})$. The combined organic phase was washed with water and brine, dried with anhydrous Na₂SO₄, and concentrated in vacuo. The residue was purified by flash column chromatograph on silica gel (petroleum ether/ethyl acetate, 20:1) to afford desired product 3a (145 mg, 73%). MS (ESI+): $m/z = 200 [M + H]^+$. ¹H NMR $(300 \text{ MHz}, \text{ CDCl}_3): \delta = 7.25-7.18 \text{ (m, 2 H, ArH)}, 7.08 \text{ (d, } J =$ 8.5 Hz, 2 H, ArH), 6.93-6.81 (m, 5 H, ArH), 5.51 (br. s, 1 H, NH),

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Scheme 3. Products and yields for Cu-catalyzed amination of aryl chloride with different nitrogen sources.

3.82 (s, 3 H, OC*H*₃) ppm. ¹³C NMR (75 MHz, CDCl₃): *δ* = 155.4, 145.4, 136.0, 129.5, 122.4, 119.8, 115.8, 114.9, 55.9 ppm.

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

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