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A Facile and Efficient Oxalyldihydrazide/Ketone-Promoted Copper-Catalyzed Amination of Aryl Halides in Water

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A novel three-component catalyst CuO/oxalyldihydrazide/hexane-2,5-dione was a very convenient, economic, and effective catalytic system for the Ullmann-type C–N coupling reaction in water. Both aryl bromides and aryl iodides could be aminated by a variety of amines even at room temperature or with heating to afford very good isolated yields.

Introduction

Many significant products (drugs, materials, optical devices, etc.), commercialized or in the development phase, possess aromatic carbon–nitrogen bonds that can be assembled by transition metal (palladium and copper) catalyzed C–N bond-formation reactions.[1] Significant improvements have been made in palladium-catalyzed C–N bond-forming processes through the development of more active catalysts in recent years.[2] However, in comparison with the use of costly palladium and toxic phosphane-containing ligands, C–N bond formation with the use of inexpensive copper catalysts in aqueous media or even in pure water would be a most attractive improvement. The copper-catalyzed Ullmann-type *N*-arylation of amines predates palladium-catalyzed amination methodology by many decades, and applications of the methodology in academic and industrial laboratories are well documented. A landmark improvement was the work of Buchwald and coworkers on the use of catalytic copper in the presence of diamino ligands.[3] Thereafter, a series of novel mono- and bidentate ligands for Cu-based C–N coupling were discovered, such as organic phosphanes,[4] N-containing aromatic heterocycles,[5] diamines,[6] diols,[7] triols,[8] *rac*-binol,[9] salicylamide,[10] β-diketones,[11] β-keto esters,[12] imines,[13] amino acids,[14] amino alcohols,[15] amino phosphates,[16] and diazaphospholane.[17] Among them, Buchwald introduced β-diketones as ligands, which made it possible to carry out the coupling of aryl iodides with aliphatic amines even at room temperature in organic media.[11a] However, a general and mild procedure for copper-catalyzed amination of aryl halides in water or aqueous media, desirable for reasons of economy and safety,[18] especially for large-scale industrial processes, has hitherto remained elusive. Moreover, other advantages, such as different selectivity from that observed in organic media, may occur in aqueous media.[18a] To the best of our knowledge, the methodologies are all substrate-limited; for example, only aryl halides containing *ortho*-carboxy substituents[19] or water-soluble amines[15b,20] could be aminated smoothly and effectively in aqueous solution.

We previously reported a typical Ullmann C–N coupling in water with utilization of bis(cyclohexanone) oxalyldihydrazone ("BCO")/copper oxide as a catalyst.[21] However, the correspondingly harsh conditions (130 °C) and the scope limitation of substrates (for example, aniline and imidazole) for *N*-arylation, as well as our curiosity about the mechanism of the reaction, prompted us to investigate further. Fortunately, we found that a three-component catalyst system, CuO/oxalyldihydrazide/ketone, facilitated various carbon–nitrogen coupling reactions in water. Herein, we wish to detail the investigation of various promoters in the copper-catalyzed amination of aryl halides and report that, promoted by oxalyldihydrazide and hexane-2,5-dione (or cyclohexanone, for benzylamine), aryl bromides or aryl iodides could successfully couple with a variety of amines and imidazoles under relatively mild conditions, and even at room temperature.

Results and Discussion

Influence of Oxalyldihydrazide and Ketones

Substantial amounts of cyclohexanone and 1,2-dicyclohexylidenehydrazine were found in the reaction mixtures of CuO/BCO-catalyzed C–N coupling reactions by GC–MS analysis. Considering the possible decomposition of BCO in aqueous base, on the one hand, we postulated that either

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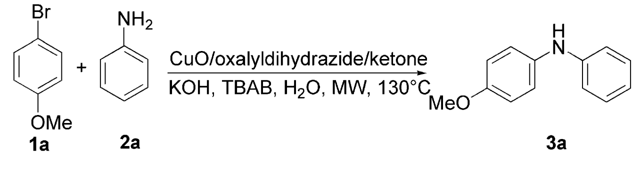
a combination of oxalyldihydrazide with cyclohexanone or a combination of hydrazine with cyclohexanone might be the actual active species of ligands for copper; on the other hand, a very significant result reported recently by Buchwald, which described a room-temperature coupling protocol with β-diketones as ligand in organic media for aryl iodides with amines,[11a] led us to assume that cyclohexanone, oxalyldihydrazide, or hydrazine might uniquely act as the actual active ligand.

To test these hypotheses, we ran our previous reaction of 4-bromoanisole with benzylamine under almost the same conditions but replaced BCO with cyclohexanone, oxalyldihydrazide, or hydrazine; unfortunately, oxalyldihydrazide was far less active than BCO, and hydrazine and cyclohexanone definitely afforded little target compound. Even 2-acetylcyclohexanone, which is one of the best ligands discovered by Buchwald, did not work under our aqueous conditions. Replacement of BCO with a combination of hydrazine and cyclohexanone also had a negative impact on the reaction, but the utilization of an equivalent amount of oxalyldihydrazide and cyclohexanone instead of BCO, fortunately, provided the desired product in 77% isolated yield. Further study showed four equivalents of cyclohexanone to be enough to convert 4-bromoanisole completely and afforded *N*-benzyl-4-methoxyaniline in 86% isolated yield. Encouraged by the result, we tried CuO/oxalyldihydrazide/cyclohexanone in a more challenging model reaction (Scheme 1). The yield increased remarkably to 63%, which is an increase of more than 10% over our prior result.[21] We then examined different mono- and diketones, which are compiled in Figure 1, as additives for the reaction of **1a** with **2a** and found substantial effects on the yields (Figure 2).



Scheme 1. Reaction of 4-bromoanisole with aniline.

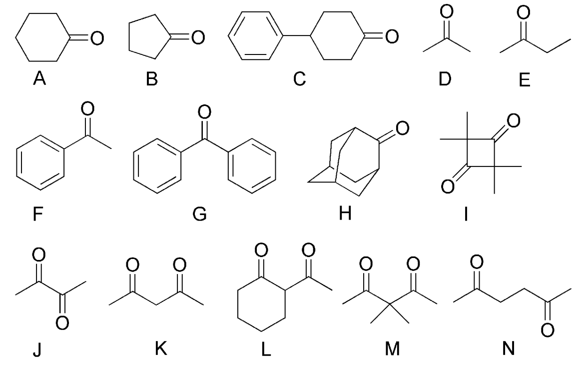


Figure 1. Ketones used for additives.

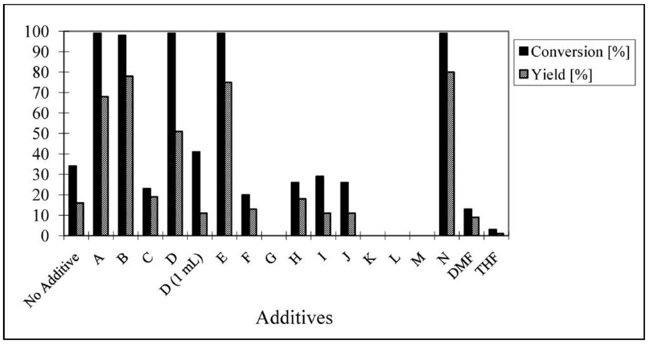


Figure 2. Effect of additives on the coupling reaction of 4-bromoanisole with aniline. Reaction conditions: 4-bromoanisole (0.5 mmol), aniline (2.0 mmol), CuO (0.125 mmol), oxalyldihydrazide (0.25 mmol), ketone (2.0 mmol for monoketones, 1.0 mmol for diketones) or DMF (0.5 mL) or THF (0.5 mL), KOH (1.0 mmol), TBAB (0.5 mmol), H_2O (1.0 mL), 130 °C, 5 min, microwave (100 W). Conversions and yields were calculated by GC.

As can be seen from Figure 2, when electron-rich monoketones with less steric hindrance (A, B, D, E) were added, the reaction provided very high conversion of 4-bromoanisole, but sometimes with problematic side reactions of debromination and hydrolysis. Adamantanone (H), a sterically hindered ketone, afforded no acceleration, as did some sort of electron-deficient monoketones (C, F) in comparison to pure oxalyldihydrazide as a ligand. Flexible β-diketones (K, L, M) and a highly electron-deficient monoketone (G) produced some negative effects and resulted in the absolute halt of the reactions. A rigid β-diketone (I) and butanedione (J) also provided no acceleration, and hexane-2,5-dione(N) was the most significant promoter of those studied, giving an 80% GC yield of the desired product.

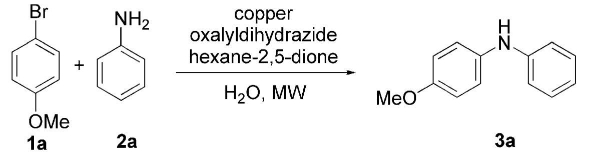
It is notable that high loading of ketones at first led us unambiguously to check if the ketones had an effect as the cosolvent or the additive. Interestingly, when DMF and THF or even acetone was used as cosolvents instead of ketone additives, the model reaction provided obvious less conversion.

Optimization of the C–N Coupling Condition

Inspired by these results, we decided to focus on hexane-2,5-dione and altered the reaction conditions to optimize the Cu sources, bases, time, temperature, phase-transfer catalysts, and the proportions among the starting materials, Cu sources, ligand, and additives with the reaction of 4-bromoanisole with aniline as a model reaction (Table 1).

As shown in Table 1, with oxalyldihydrazide as a ligand and hexane-2,5-dione as an additive, all kinds of copper sources were effective in promoting the reaction (Table 1, Entries 5–11) and CuO proved to be the best one. Remarkably, when the catalyst loading was decreased from 25 mol-% to 5 mol-%, the reaction proceeded very well (Table 1, Entries 2, 5, 15), and even down to 1.25 mol-% loading of CuO, the yield was only slightly decreased (Table 1, Entry 16). Moreover, several bases with different basicities led to similar efficiencies of the reaction, and KOH was found to be the most appropriate one (Table 1, Entries 5, 12–14). However, for the model reaction, more investigation indicated that if the loading of oxalyldihydrazide, hexane-2,5-dione, TBAB, or aniline was reduced excessively, the conversion of 4-bromoanisole did not change, but the yield of the target product decreased because of the increase of side products resulting from debromination and hydrolysis of 4-bromoanisole. In addition, the reaction temperature (120 °C) was good enough to realize the reaction (Table 1, Entries 1–3).

Table 1. Copper/oxalohydrazide/hexane-2,5-dione catalyzed *N*-arylation of 4-bromoanisole with aniline under different conditions.[a]



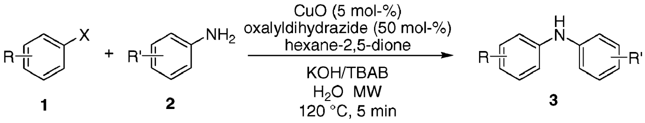
Entry	Catalyst [mol-%][b]	Base[equiv][b]	T [°C]	Conversion [%] / Yield [%][c]
1	CuO (25)	KOH (2)	130	100/75
2	CuO (25)	KOH (2)	120	99/76
3	CuO (25)	KOH (2)	110	96/70
4	CuO (25)	KOH (1.5)	120	87/61
5	CuO (10)	KOH (2)	120	100/75
6	Cu_2O (10)	KOH (2)	120	97/75
7	CuI (10)	KOH (2)	120	99/59
8	$CuSO_4$ (10)	KOH (2)	120	61/35
9	$CuCl_2$ (10)	KOH (2)	120	81/46
10	$Cu(OAc)_2$ (10)	KOH (2)	120	95/64
11	Cu (10)	KOH (2)	120	88/59
12	CuO (10)	K_2CO_3 (2)	120	99/71
13	CuO (10)	K_3PO_4 (2)	120	95/71
14	CuO (10)	Cs_2CO_3 (2)	120	98/66
15	CuO (5)	KOH (2)	120	100/85
16	CuO (1.25)	KOH (2)	120	98/84
17	CuO (0.6)	KOH (2)	120	57/40

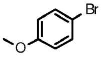
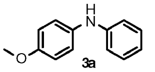
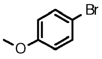
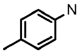
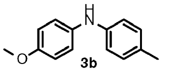
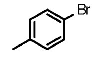
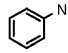
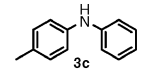
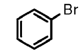
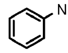
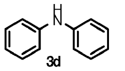
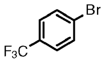
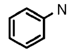
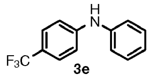
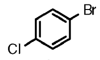
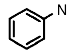
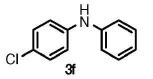
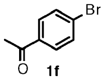
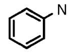
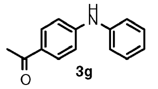
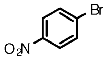
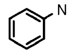
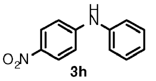
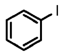
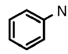
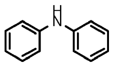
[a] Reaction conditions: 4-bromoanisole (0.5 mmol), aniline (2.0 mmol), catalyst, oxalyldihydrazide (0.25 mmol), hexane-2,5-dione (0.5 mmol), base, TBAB (0.125 mmol), H_2O (1.0 mL), microwave (100 W), 5 min. [b] Relative to 4-bromoanisole. [c] Calculated by GC.

Microwave-Assisted Coupling Reactions of Aryl Halides with Anilines

To establish the generality of this protocol, a variety of functionalized aryl halides were coupled with anilines under the optimized condition [CuO (5 mol-%), oxalyldihydrazide (50 mol-%), TBAB (25 mol-%), hexane-2,5-dione (1.0 equiv.), KOH (2.0 equiv.), H_2O, 120 °C, 5 min]. Some conclusions could be drawn from Table 2. CuO/oxalyldihydrazide/hexane-2,5-dione is an exceptionally good catalytic system for the reaction of aryl halides with anilines in water. Both aryl bromides with electron-rich *para* substituents and neutral aryl bromides reacted with anilines to afford good isolated yields (Table 2, Entries 1–4). The traditionally activated aryl bromides reacted with aniline under our reaction condition to provide desired products with slightly lower isolated yields (Table 2, Entries 5–8) for different reasons: For the reaction of 1-bromo-4-(trifluoromethyl)benzene with aniline (Table 2, Entry 5), the lower yield was due to a large amount of unreacted starting material, but the reaction of 1-bromo-4-chlorobenzene with aniline (Table 2, Entry 6) provided very high conversion (96% by GC analysis) with some side products of debromination (13% in GC yield) and hydrolysis (14% in GC yield). Aryl iodides are generally accepted as being more reactive than aryl bromides; hence, under our reaction conditions, the reaction of iodobenzene with aniline gave a slightly lower yield than bromobenzene because of some side reactions (Table 2, Entries 4 and 9).

Table 2. Microwave-assisted CuO/oxalyldihydrazide/ketone-catalyzed coupling reactions of aryl halides with anilines in water.[a]



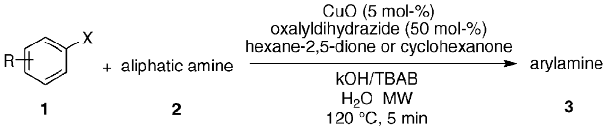
Entry	ArX	Amine	Product	Yield [%][b]
1	 1a	 2a	 3a	78
2	 1a	 2b	 3b	75
3	 1b	 2a	 3c	70
4	 1c	 2a	 3d	75
5	 1d	 2a	 3e	45
6	 1e	 2a	 3f	58
7	 1f	 2a	 3g	66
8	 1g	 2a	 3h	56
9	 1h	 2a	 3d	63

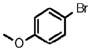
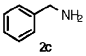
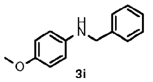
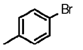
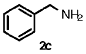
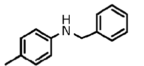
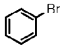
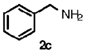
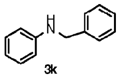
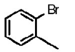
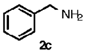
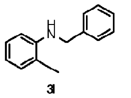
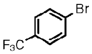
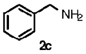
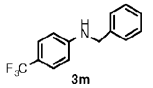
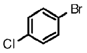
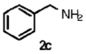
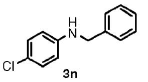
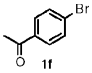
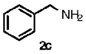
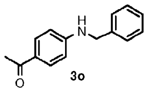
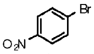
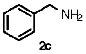
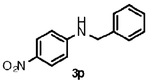
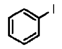
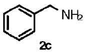
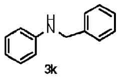
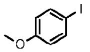
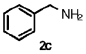
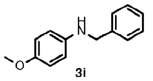
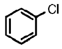
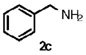
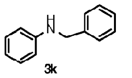
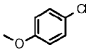
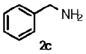
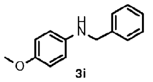
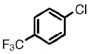
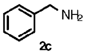
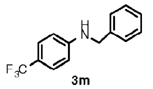
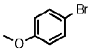
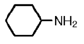
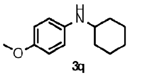
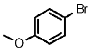
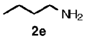
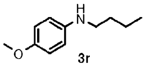
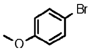
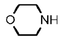
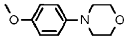
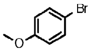
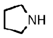
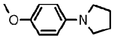
[a] Reaction conditions: ArX (0.5 mmol), amine (2.0 mmol), CuO (0.025 mmol), oxalyldihydrazide (0.25 mmol), hexane-2,5-dione (0.5 mmol), KOH (1.0 mmol), TBAB (0.125 mmol), H_2O (1.0 mL), 120 °C, 5 min, microwave (100 W). [b] Isolated yield.

Microwave-Assisted Coupling Reactions of Aryl Halides with Aliphatic Amines

When the coupling reactions of various aryl halides with benzylamine and aliphatic primary amines were examined, cyclohexanone was used instead of hexane-2,5-dione to

Table 3. Microwave-assisted CuO/oxalyldihydrazide/ketone-catalyzed coupling reactions of aryl halides with aliphatic amines in water.[a]



Entry	ArX	Amine	Product	Ketone	Yield [%][b]
1	 1a	 2c	 3i	N A	82 91
2	 1b	 2c	 3j	A	85
3	 1c	 2c	 3k	A	80
4	 1i	 2c	 3l	A	65[c]
5	 1d	 2c	 3m	A	79
6	 1e	 2c	 3n	A	86
7	 1f	 2c	 3o	A	84
8	 1g	 2c	 3p	A	63
9	 1h	 2c	 3k	A	86
10	 1j	 2c	 3i	A	86
11	 1k	 2c	 3k	A	trace
12	 1l	 2c	 3i	A	trace
13	 1m	 2c	 3m	A	trace
14	 1a	 2d	 3q	A	76
15	 1a	 2e	 3r	A	74
16	 1a	 2f	 3s	N	60
17	 1a	 2g	 3t	N	50[d]

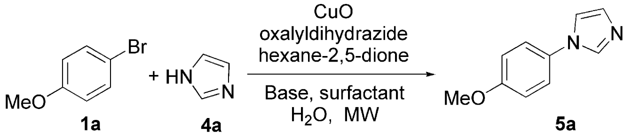
[a] Reaction conditions: ArX (0.5 mmol), amine (2.0 mmol), CuO (0.025 mmol), oxalyldihydrazide (0.25 mmol), hexane-2,5-dione (N, 0.5 mmol) or cyclohexanone (A, 2 mmol), KOH (1.0 mmol), TBAB (0.125 mmol), H_2O (1.0 mL), 120 °C, 5 min, microwave (100 W). [b] Isolated yield. [c] CuO (0.1 mmol). [d] GC yield 64%, debromination product, 34%.

avoid an unexpected Paal–Knorr reaction to consume benzylamine and hexane-2,5-dione and decrease the yield of target product (Table 3, Entry 1). These results are summarized in Table 3. All aryl bromides and aryl iodides reacted with benzylamine to afford good-to-excellent isolated yields up to 91%, although *o*-bromotoluene provided a little lower yield (Table 3, Entry 4) due to steric hindrance, but these optimized conditions are not effective to aryl chlorides (Table 3, Entry 11–13). In addition, linear and cyclic aliphatic amines were all feasible, but secondary amines gave slightly lower yields because of problematic debromination of aryl bromides (Table 3, Entries 16 and 17).

Microwave-Assisted Coupling Reactions of Aryl Halides with Imidazoles

However, in comparison with benzylamine, anilines, and aliphatic amines, it was slightly more difficult for nitrogen-containing heterocyclic aromatic compounds, such as imidazoles, to undergo the *N*-arylating reactions. So, a general and mild procedure for copper-catalyzed C–N bond formation of aryl halides with imidazoles has remained relatively scarce, not to mention the reaction in water. To extend the applicability of the CuO/oxalyldihydrazide/ketone catalytic system, the coupling reaction of imidazole with 4-bromoanisole in water was investigated (Table 4). The reaction ran successfully under the optimized conditions, but with an increase in the reaction temperature to 140 °C, and the desired product was isolated in 82% yield (Table 4, Entry 2). Modification with utilization of K_3PO_4 instead of KOH led to the isolation of 1-(4-methoxyphenyl)-1*H*-imidazole in up to 89% yield (Table 4, Entry 6).

Table 4. Effects of reaction conditions on the coupling reaction of 4-bromoanisole with imidazole.[a]

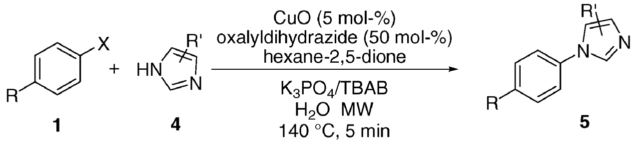


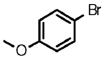
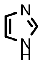
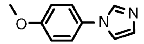
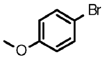
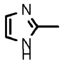
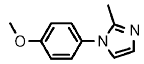
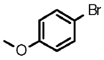
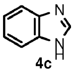
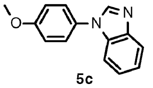
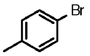
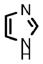
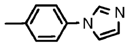
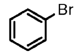
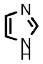
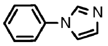
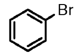
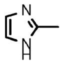
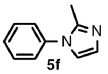
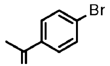
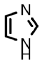
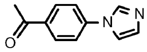
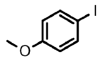
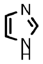
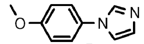
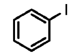
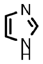
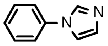
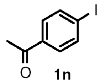
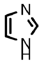
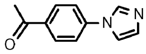
Entry	Base [equiv.][b]	Temperature [°C]	Yield [%][c]
1	KOH (2)	130	70
2	KOH (2)	140	82
3	KOH (2)	150	74
4	Cs_2CO_3 (2)	140	78
5	K_2CO_3 (2)	140	78
6	K_3PO_4 (2)	140	89
7	K_3PO_4 (1.5)	140	80
8	K_3PO_4 (2)	130	77

[a] Reaction conditions: 4-bromoanisole (0.5 mmol), imidazole (2.0 mmol), CuO (0.025 mmol), oxalyldihydrazide (0.25 mmol), hexane-2,5-dione (0.5 mmol), base, TBAB (0.125 mmol), H_2O (1.0 mL), 5 min microwave (100 W). [b] Relative to 4-bromoanisole. [c] Isolated yield.

To establish the generality of this protocol, a variety of aryl halides with different substituents were aminated with imidazoles under the optimized condition (Table 5). The results showed that CuO/oxalyldihydrazide/hexane-2,5-dione is also a very effective catalytic system for the *N*-arylation reaction of imidazoles in water. Imidazole and 2-methyl-1*H*-imidazole reacted with aryl halides to afford good-to-excellent yields (Table 5, Entries 1, 2, 4–10), but 1*H*-benzo[*d*]imidazole gave only a fair yield, because a large amount of starting material was left unreacted (Table 5, Entry 3).

Table 5. Microwave-assisted CuO/oxalyldihydrazide/hexane-2,5-dione-catalyzed coupling reactions of aryl halides with imidazoles in water.[a]



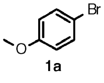
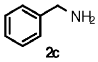
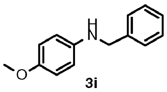
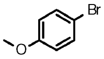
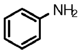
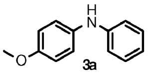
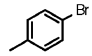
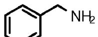
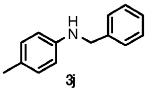
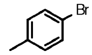
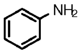
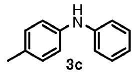
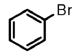
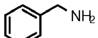
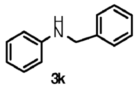
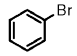
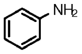
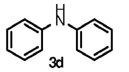
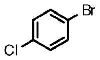
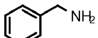
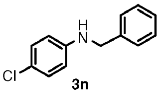
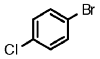
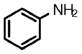
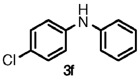
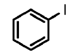
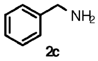
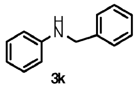
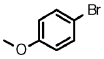
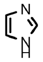
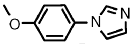
Entry	ArX	Imidazoles	Product	Yield [%][b]
1	 1a	 4a	 5a	89
2	 1a	 4b	 5b	70
3	 1a	 4c	 5c	52
4	 1b	 4a	 5d	76
5	 1c	 4a	 5e	83
6	 1c	 4b	 5f	67
7	 1f	 4a	 5g	77
8	 1j	 4a	 5a	77
9	 1h	 4a	 5e	88
10	 1n	 4a	 5g	84

[a] Reaction conditions: ArX (0.5 mmol), amine (2.0 mmol), CuO (0.025 mmol), oxalyldihydrazide (0.25 mmol), hexane-2,5-dione (0.5 mmol), K$_3$PO$_4$ (1.0 mmol), TBAB (0.125 mmol), H$_2$O (1.0 mL), 140 °C, 5 min, microwave (100 W). [b] Isolated yield.

Coupling Reactions of Aryl Halides with Amines under Conventional Heating Conditions

The scope of the reactions extended to conventional heating mode successfully (Table 6). At first, we conducted the model reaction (Scheme 1) in a preheated oil bath in a sealed vial at 120 °C and obtained 75% yield of isolated product (Table 6, Entry 2). It is interesting to note that when we performed the coupling reactions at 90 °C (reflux) in a conventional oil bath, the reactions gave good-to-excellent yields only when the reaction time was increased from 5 min to 8 h. These results would benefit organic chemists to develop a C–N coupling reaction in water for industrial purposes.

Table 6. CuO/oxalyldihydrazide/ketone-catalyzed coupling reactions of aryl halides with amines in water under conventional heating conditions.[a]

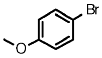
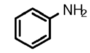
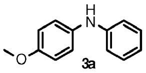
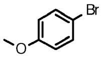
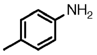
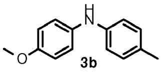
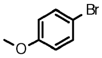
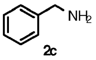
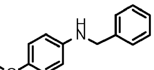
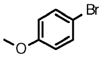
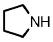
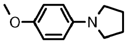
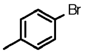
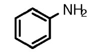
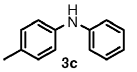
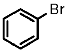
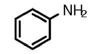
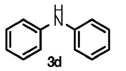
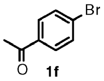
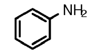
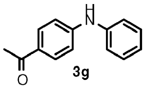
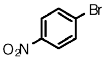
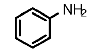
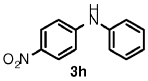
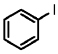
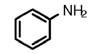
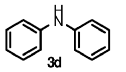
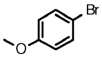
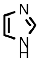
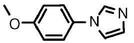
Entry	ArX	Amine	Product	Ketone	Yield [%][b]
1	 1a	 2c	 3i	A	88
2	 1a	 2a	 3a	N	69 75[c]
3	 1b	 2c	 3j	A	85
4	 1b	 2a	 3c	N	70
5	 1c	 2c	 3k	A	75
6	 1c	 2a	 3d	N	70
7	 1e	 2c	 3n	A	69
8	 1e	 2a	 3f	N	59
9	 1h	 2c	 3k	A	90
10	 1a	 4a	 5a	N	87[d]

[a] Reaction conditions: ArX (1.0 mmol), amine (4.0 mmol), CuO (0.05 mmol), oxalyldihydrazide (0.5 mmol), cyclohexanone (A, 4 mmol) or hexane-2,5-dione (N, 1.0 mmol), KOH (2.0 mmol), TBAB (0.25 mmol), H$_2$O (6.0 mL), 90 °C, 8 h. [b] Isolated yield. [c] Sealed vial in oil bath, 120 °C. [d] K$_3$PO$_4$ in place of KOH, reflux.

Coupling Reactions of Aryl Halides with Amines at Room Temperature

We ran our model reaction under almost the same conditions, but at room temperature. It is noteworthy that the model reaction proceeded equally well with an increase in the catalyst loading to 20 mol-% and a prolonged reaction time of 96 h. An 86% isolated yield of the desired product was obtained, which is slightly higher than those obtained with heating (Table 7, Entry 1). To prove the applicability of this protocol, several functionalized aryl bromides and aryl iodides were aminated and provided good-to-excellent yields (Table 7). It should be noted that the reactions failed with cyclohexanone as a promoter at room temperature, even though cyclohexanone was effective for the *N*-arylation of benzylamine under thermal treatment. Moreover, arylation of imidazole did not work because of the poor conversion of the aryl bromide.

Table 7. CuO/oxalyldihydrazide/acetonyl acetone catalyzed coupling reaction of aryl halides with amines in water at room temperature.[a]

Entry	ArX	Amine	Product	Time [h]	Yield [%][b]
1	 1a	 2a	 3a	96 (72) (48)	86 (74) (33)
2	 1a	 2b	 3b	96	83
3	 1a	 2c	 3i	96	81 (trace[c])
4	 1a	 2g	 3t	96	42
5	 1b	 2a	 3c	96	77
6	 1c	 2a	 3d	96	76
7	 1f	 2a	 3g	96	66
8	 1g	 2a	 3h	72	64
9	 1h	 2a	 3d	96	92
10	 1a	 4a	 5a	96	trace

[a] Reaction conditions: ArX (0.5 mmol), amine (2.0 mmol), CuO (0.1 mmol), oxalyldihydrazide (0.25 mmol), hexane-2,5-dione (0.5 mmol), KOH (1.0 mmol), TBAB (0.125 mmol), H_2O (1.0 mL), 25 °C. [b] Isolated yield. [c] Cyclohexanone (2.0 mmol) instead of hexane-2,5-dione (0.5 mmol) was used.

Conclusions

We primarily proved that the BCO/CuO catalytic system is a precatalyst, in which BCO is decomposed in situ into oxalyldihydrazide and cyclohexanone. On the basis of this discovery, we, for the first time, established a novel three-component catalyst, CuO/oxalyldihydrazide/hexane-2,5-dione, for C–N coupling in water at room temperature, which can be performed under microwave irradiation or under conventional heating. A variety of amines including N-containing aromatic heterocycles could be *N*-arylated with aryl halides effectively under corresponding experimental conditions. In addition, four important discoveries were also preliminarily established: (1) The loading of the catalyst could be very low (down to less than 1.25 mol-%). (2) Unactivated aryl halides possess high reactivity. (3) Monoketones and diketones, but not β-diketones (e.g. 2-acetylcyclohexanone, which was one of the best ligands discovered by Buchwald, did not work in water), promoted the catalytic potential of CuO/oxalyldihydrazide in water. This discovery will benefit the future study of the mechanical differences between Cu-catalyzed C–N coupling in organic media and in water. (4) Electron-rich ketones are better than their electron-deficient counterparts for C–N bond formation in water under our reaction conditions. These discoveries will benefit the future design of novel, efficient, and environmentally benign Cu-based catalysts for C–N cross-coupling reactions.

Experimental Section

General Conditions: All aryl halides and amines were commercially available and used as received. All reactions were carried out on the CEM discover system (Model NO. 908010, manufactured by CEM Company in USA, with vertically-focused IR temperature control system, maximum microwave power 300 W, frequency @ 2.455 GHz) in vials (size: 10 mL) sealed with a septum with a stirring option. Flash column chromatography was performed with silica gel (200–300 mesh). Thin-layer chromatography was carried out with Merck silica gel $60F_{254}$ plates. All yields reported in the publication represent an average of at least two independent runs. All products were characterized by MS and ^{1}H NMR spectroscopy, and this data was compared to the previously reported data. ^{1}H NMR spectra were recorded at room temperature with a Mercury-Plus 300 instrument with TMS as an internal reference. LC–MS were run with a LCMS-2010A. GC–MS were run with a Voyager GC–MS instrument with an electron impact (70 eV) mass selective detector. EI mass spectra were recorded with a Thermo DSQ mass spectrometer. FAB mass spectra were recorded with a VGA-ZAB-HS instrument. Elemental analyses were perfomed with a Vario EL instrument. All compounds have been reported previously and characterized by comparison with their reported data.

General Procedure for the Microwave-Assisted Coupling Reaction. Synthesis of 3a: A 10-mL vessel was charged with CuO (2 mg, 0.025 mmol), oxalyldihydrazide (30 mg, 0.25 mmol), hexane-2,5-dione (57 mg, 0.5 mmol), 4-bromoanisole (**1a**; 94 mg, 0.5 mmol), aniline (**2a**; 186 mg, 2 mmol), TBAB (40 mg, 0.125 mmol), H_2O (1.0 mL), and a magnetic stir bar. The vessel was sealed with a septum and placed into the single-mode microwave cavity. The reaction temperature was raised from room temperature to 120 °C over 1 min, and then the reaction mixture was held at this temperature for 5 min. After allowing the mixture to cool to room temperature, the reaction mixture was extracted with ethyl acetate (3 × 40 mL). The combined organic phase was washed with water and brine, dried with anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatograph on silica gel (ethyl acetate/petroleum ether, 1:20) to afford **3a** as a white solid (78 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.11 (t, J = 7.8 Hz, 2 H), 6.98 (d, J = 8.7 Hz, 2 H), 6.83–6.74 (m, 5 H), 5.45 (br. s, 1 H), 3.71 (s, 3 H) ppm. MS (ESI+): m/z (%) = 200 [M + H]$^+$. $C_{13}H_{13}NO$ (199.25): calcd. C 78.36, H 6.58, N 7.03; found C 78.06, H 6.62, N 6.97.

General Procedure for the Coupling Reaction Heated with an Oil Bath. Synthesis of 3i: To a 15-mL flask was added CuO (4 mg, 0.05 mmol), oxalyldihydrazide (59 mg, 0.5 mmol), cyclohexanone (196 mg, 2 mmol), 4-bromoanisole (**1a**; 187 mg, 1.0 mmol), benzylamine (**2c**; 428 mg, 4 mmol), KOH (112 mg, 2.0 mmol), TBAB (80 mg, 0.25 mmol), H_2O (6.0 mL), and a magnetic stir bar. The reaction mixture was stirred at 90 °C in an oil bath for 8 h. After allowing the mixture to cool to room temperature, the reaction mixture was extracted with ethyl acetate (3 × 40 mL). The combined organic phase was washed with water and brine, dried with anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatograph on silica gel (ethyl acetate/petroleum ether, 1:30) to afford **3i** as a white solid (187 mg, 88%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.14 (m, 5 H), 6.68 (d, J = 9.0 Hz, 2 H), 6.51 (d, J = 9.0 Hz, 2 H), 4.19 (s, 2 H), 3.65 (s, 3 H) ppm. MS (ESI+): m/z (%) = 214 [M + H]$^+$. $C_{14}H_{15}NO$ (213.28): calcd. C 78.84, H 7.09, N 6.57; found C 78.73, H 7.15, N 6.49.

General Procedure for the Coupling Reaction Performed at Room Temperature. Synthesis of 3d: To a 10-mL vessel was added CuO (8 mg, 0.1 mmol), oxalyldihydrazide (30 mg, 0.25 mmol), hexane-2,5-dione (57 mg, 0.5 mmol), iodobenzene (**1h**; 102 mg, 0.5 mmol), aniline (**2a**; 186 mg, 2 mmol), KOH (56 mg, 1.0 mmol), TBAB (40 mg, 0.125 mmol), H_2O (1.0 mL), and a magnetic stir bar. The reaction mixture was stirred at room temperature (25 °C) for 96 h. The reaction mixture was extracted with ethyl acetate (3 × 40 mL). The combined organic phase was washed with water and brine, dried with anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatograph on silica gel (ethyl acetate/petroleum ether, 1:20) to afford diphenylamine as a pale-yellow solid (78 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.18 (t, J = 7.5 Hz, 4 H), 6.98 (d, J = 7.8 Hz, 4 H), 6.84 (t, J = 7.5 Hz, 2 H), 5.66 (br. s, 1 H) ppm. MS (ESI+): m/z (%) = 170 [M + H]$^+$. $C_{12}H_{11}N$ (169.22): calcd. C 85.17, H 6.55, N 8.28; found C 84.92, H 6.56, N 8.18.

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

Acknowledgments

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