D-Glucose: An Efficient Reducing Agent for a Copper(II)-Mediated Arylation of Primary Amines in Water

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A copper-catalyzed Ullmann-type amination with primary amines in water with a combination of copper(II) triflate [Cu(OTf)₂], dipivaloylmethane, and D-glucose is reported. The mild conditions and the use of an inexpensive catalyst as well as a renewable feedstock (D-glucose and the surfactant TPGS-750-M, which is derived from vitamin E) make this protocol a safe and convenient strategy for efficient C–N bond formation. This easy-to-handle procedure is extremely competitive compared to palladium-based reactions and may be used to synthesize N-containing molecules, such as drugs or organic light-emitting diodes (OLEDs).

Introduction

Transition-metal-catalyzed reactions have a prominent place in the arsenal of synthetic chemists.^[1] These reactions have traditionally been performed in conventional organic solvents. Currently, the design of sustainable protocols involving green catalysis is emphasized.^[2] The use of water as a solvent has many advantages because it is the most economical, safe, and environmentally friendly solvent.^[3] The formation of micelles in the presence of the nonionic amphiphile polyoxyethanyl-atocopheryl succinate (TPGS-750-M) helps solubilize organic reagents.^[4a] The viability of this surfactant-promoted chemistry was demonstrated by Lipshutz et al. Indeed, in 2008, they reported the use of this new methodology for metathesis^[4] and important cross-coupling reactions such as Suzuki-Miyaura,^[4a,d,e,5] Heck,^[4d-f,6] C–H activation,^[4a,e] Sonogashira,^[4a,7] and Buchwald-Hartwig reactions.^[4a,e,8] Recently, our group further investigated the Buchwald-Hartwig reaction,^[9] as the formation of C-N bonds is one of the most useful reaction types in medicinal chemistry and materials science.^[10] Thus, we reported a universal catalytic system for Buchwald-Hartwig reactions under micellar conditions.^[11] However, the industrial use of

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Supporting Information for this article can be found under: http://dx.doi.org/10.1002/cssc.201600801. these methods may be limited by the high cost, scarcity, and toxicity of palladium. As an alternative, copper-based Ullmann aminations attracted our attention owing to the low cost, low toxicity, and high abundance of copper.

Copper-mediated arylation was discovered several decades before the Buchwald-Hartwig reaction, but its use was limited for a long time because several drawbacks restricted its industrial application. Originally, it required stoichiometric amounts of copper, high reaction temperatures, and high-boiling-point polar solvents.^[12] Moreover, the scope of the reaction was also restricted to electron-poor aromatic substrates.^[13a-c] In 2001, the discovery of new copper/bidentate-ligand systems led to a spectacular renewed interest in Ullmann reactions.^[10b, 13] The milder conditions of the new copper-catalyzed aminations enlarged the scope in terms of substrate tolerance, chemoselectivity, and enantioselectivity.^[13e, 14] Despite the emergence of green chemistry, copper-catalyzed coupling reactions with water as the solvent have been described only rarely. Only a few examples of copper-catalyzed N-arylation in aqueous media have been reported with heterocyclic amines,[15a-I] aliphatic amines,^[15g-h,l,n] amino acids,^[15h,m] or ammonia.^[15n,o] To be efficient, these reactions required temperatures between 80 and 130 °C. Herein, we describe an efficient and highly selective copper-catalyzed N-arylation or heteroarylation with primary amines under micellar conditions at much lower temperatures [room temperature (RT, 25 $^{\circ}$ C) or 50 $^{\circ}$ C].

Results and Discussion

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In our initial screening experiments, 3-iodotoluene (**1 a**) and 3phenylpropylamine (**2**) were used as model substrates to establish the most suitable conditions (Figure 1). Seven commercially available classical ligands such as β -diketones, diamines, and phenanthroline were tested with Cul (10%) as the catalyst. NaOtBu was selected as a suitable base, and the reactions were performed in water supplemented with TPGS-750-M





Figure 1. Impact of various ligands in the copper-catalyzed amination of 3iodotoluene in TPGS-750-M in the presence or absence of NaAsc. Reaction conditions: Cul (10 mol%), ligand (20 mol%), NaOtBu (2 equiv.), 3-iodotoluene (1 equiv.), 3-phenylpropylamine (1.2 equiv.), TPGS-750-M (2 wt%), 50 °C, 24 h. [a] Average yield of two experiments. Yields were determined by HPLC with a UV detector and benzophenone as an external standard. W/L: without ligand.

(2 wt%) as the surfactant. In the absence of ligand (W/L), no reaction was observed, and the nitrogen-based ligands (L3–L7) were poorly active or inactive. Both β -diketones dipivaloylmethane (L1, THMD) and 2-isobutyrylcyclohexanone (L2) showed promising effects and afforded the product in approximately 25% yield. To explain this modest yield, we could consider the possible oxidation of the copper(I) catalyst to form an inactive copper(II) species in water. To validate this hypothesis, a reduc-

ing agent was added to regenerate the copper(I) catalyst in situ. Sodium ascorbate (NaAsc) was chosen for its ability to reduce copper(II) and its well-known use in the "click" reaction.^[16] It is also often used for cross-coupling arylations with ammonia,^[150] amides,^[17] and disulfides.^[18] Significantly improved yields (50%) were obtained in the presence of NaAsc with the β -diketone ligands L1 and L2 (Figure 1). This result encouraged us to favor the use of copper(II) catalysts in the presence of reducing agents.

The influences of eight different copper(II) salts and leaving groups were studied in combination with either L1 or L2 (Figure 2). Surprisingly, for L1, bromo derivatives appeared systematically more reactive than the corresponding iodo ones. This result was quite unexpected because bromoaryls are generally less reactive in Ullmann-type reactions than iodo derivatives. In contrast, L2 appeared systematically more effective with 3-iodotoluene (**1a**) than with 3-bromotoluene (**1b**).

However, it is important to note that the yields for L2 never exceeded 50%, whereas L1 led to yields greater than 70%. Further explorations revealed the nonefficacy of chloro, *O*-triflate, and *O*-tosylate leaving groups. Although copper(II) oxide showed a modest activity, the other copper(II) salts, that is, copper(II) triflate [Cu(OTf)₂], Cu(NO₃)₂·3 H₂O, and CuBr₂, afforded good yields of up to 75% yield. On the basis of these results, we selected **1b** with L1 in combination with Cu(OTf)₂, Cu(NO₃)₂·3H₂O, or CuBr₂ to continue our study.

We have previously highlighted the importance of reducing agents in this copper-catalyzed amination under micellar conditions. Without a reducing agent, no reaction was observed with the copper(II) catalyst (Supporting Information, Figure S2). To optimize this parameter, three classical reducing agents were used [sodium ascorbate, hydroquinone, and tris(2-carboxyethyl)phosphine (TCEP)] as well as three reducing sugars (D-glucose, D-fructose, and D-galactose) at two different temperatures (RT and 50 °C, Figure 3 and Figure S1). In the presence of Cu(OTf)₂, no reaction was observed with TCEP at both temperature or with NaAsc at room temperature. All other reducing agents led to the desired product **3 b** in moderate-to-excellent yields, even at room temperature. In particular,



Figure 2. Impact of copper(II) salts and leaving groups in combination with either L1 or L2. Reaction conditions: copper(II) salt (10 mol%), L1 or L2 (20 mol%), NaAsc (10 mol%), NaOtBu (2 equiv.), ArX (1 equiv.), 3-phenylpropylamine (1.2 equiv.), TPGS-750-M (2 wt%), 50 °C, 24 h. [a] Average yield of two experiments. Yields were determined by HPLC with a UV detector and benzophenone as an external standard.

ChemSusChem 2016, 9, 1-7

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Figure 3. Screening of reducing agents. Reaction conditions: $Cu(OTf)_2$ (10 mol%), L1 (20 mol%), reducing agent (10 mol%), NaOtBu (2 equiv.), 3-bromotoluene (1 equiv.), 3-phenylpropylamine (1.2 equiv.), TPGS-750-M (2 wt%), 50 °C or RT, 24 h. [a] Average yield of two experiments. Yields were determined by HPLC with a UV detector and benzophenone as an external standard.

D-glucose afforded the desired product in 84% yield at room temperature. Similar results were obtained with Cu(NO₃)₂.3H₂O and CuBr₂ in the presence of sodium ascorbate and D-glucose. However, the Cu(OTf)₂L1/D-glucose catalytic system was the best combination for this green Ullmann-type amination. To the best of our knowledge, p-glucose has been used rarely as a reducing agent in organic chemistry. It has been reported for the one-pot assembly of N-fused imidazoles,^[19] the reductive homocoupling of aryl halides,^[20] and the formation of quinolines involving a three-steps cascade.^[21] Therefore, this seems to be the first report of the use of D-glucose as a reducing agent in a copper-catalyzed reaction in an aqueous medium. Its abundance and nontoxicity make D-glucose the perfect additive for sustainable chemistry approaches. This aspect is strengthened by the efficiency of the Cu(OTf)₂L1/D-glucose catalytic system at room temperature, which is a positive parameter in terms of energy saving.

Several other parameters were further evaluated including different bases (Figure S3), various β -diketones (Figure S4), the Cu/ligand ratio (Figure S5), the catalyst loading (Figure S5), the molar ratio of the reducing agent (Figure S2), the surfactant (Figure S6), the quantity of surfactant (Figure S7), and the atmosphere (Figure S8). On the basis of the results from all of these experiments, a combination of Cu(OTf)₂ (10 mol%), L1 (20 mol%), D-glucose (10 mol%), and NaOtBu (2 equiv.) was selected as the best catalytic system to perform this Ullmann-type amination at room temperature in an aqueous medium supplemented with TPGS-750-M (2 wt%).

With the optimal conditions in hand, the scope of the reaction was investigated with a diverse set of substituted amines and aryl or heteroaryl bromides. The results are summarized in Figure 4. The reaction was efficient for aryl bromides with either electron-donating groups at the *ortho* (**3ca**), *meta* (**3a**, **3b**, **3cb**, and **3n**), or *para* (**3cc**, **3d**, and **3e**) position or electron-withdrawing groups (**3f-m**, **3o-q**). For a bulky substituent at the *ortho* position of the aryl bromide (**3ca**), the reaction needed to be heated to 50° C to obtain a yield of 48%. For aryl rings bearing bromine and chlorine substituents (3 f and 4e), the reaction only occurred at the brominated position. It is particularly noteworthy that the reaction proceeds successfully to provide the desired products in moderate-tohigh yields without the protection of the functional group, even in the presence of sensitive substituents [i.e., CN (3i), CONH₂ (**3j**), CO₂tBu (**3k**), MeCO (**3I**), CHO (**3m**), or nitro (**3o**)]. Starting from an acetal moiety, the aminated product 3n was isolated as the sole product from the reaction at RT. However, at 50 °C, a partial deprotection of the acetal was observed, and the corresponding aldehyde 3mb formed in 22% yield. We then turned our attention to various bromoheterocyclic systems such as pyridine (4a-e), pyrimidine (4f and 4g), pyrazine (4h), and thiophene (4i), which were efficiently N-arylated with numerous primary amines (Figure 4). If the bromine atom was at the meta position, the reaction proceeded under the optimized conditions (2 wt% of TPGS-750-M at RT) with good-toexcellent yield, even with a strongly hindered amine (4c and 4d). Good yields were also obtained with 2-bromopyrazine, 2bromopyrimidine, and 3-bromothiophene (4h, 4f, and 4i). Unfortunately, no reaction was observed with iminochlorides such as 2-chloropyridine. Next, a representative series of cyclohexylor piperidinyl-containing amines were used with different steric bulk at the amino group (3t-x). As illustrated in Figure 4, the reaction proceeded even with bulky α -branched primary amines, but it is necessary to work at 50 °C to reach 60% yield (3x-y). Interestingly, for substrates bearing both primary and secondary amine moieties, only the primary amine reacted (3za and 3zb).

As shown in Figure 4, our methodology is compatible with free hydroxy functions. Starting from 4-bromobenzyl alcohol, the N-coupling product with phenylpropylamine was formed in 74% yield at RT (**3 d**, 74%). The yield could be increased slightly at 50°C. Unfortunately, no reaction was observed with 3-aminopropanol, even in the presence of an excess of amine.



Figure 4. Expanded scope of amination with aryl bromides. Reaction conditions : Cu(OTf)₂ (10 mol%), L1 (20 mol%), d-glucose (10 mol%), NaOtBu (2 equiv.), ArBr (1 equiv.), RNH₂ (1.2 equiv.), TPGS-750-M (2 wt%), RT, 24 h. [a] Yields refer to isolated product. [b] Previously unreported products were characterized by NMR spectroscopy and HRMS. [c] TPGS-750-M (5 wt%). [d] Reaction performed at 50 °C. [e] RNH₂ (5 equiv.). [f] RNH₂ (3 equiv.). [g] 22% of **3 mb**. n.r.: no reaction.

The lack of reaction may be explained by the chelation of the aminoalcohol to the copper center. To verify this hypothesis, the same reaction was performed with 6-aminohexan-1-ol, a higher homologue, and we were pleased to isolate the expected coupling product in a satisfactory yield (3sb, 60%). If the alcohol was protected as an ether group, the desired product 3sc was obtained with a moderate yield of 61%. No reaction was observed with other amines such as anilines, secondary amines, or benzamides. From 4-bromobenzonitrile, the corresponding product 3i was formed in a yield of only 29% owing to the poor solubility of the reactant. We overcame this issue by using either 5 wt% of TPGS-750-M at RT or 2 wt% of TPGS-750-M at 50 °C, which improved the yield to 87 and 71 %, respectively. The same conditions were applied with (3,4,5-trifluorophenyl)methylamine (3gb), 2-bromopyridine (4a and 4b), and 5-bromopyrimide (4g) to overcome the solubility issues. In contrast, for a highly water-soluble amine, such as n-propylamine, an excess of amine was needed (5 equiv.) to reach a yield of 67% (3r).

In the absence of surfactant, our model reaction was still successful, and 75% yield was obtained instead of 85% with TPGS-750-M (2%, see Figure S7). This important result shows that this copper-catalyzed reaction is likely to occur in water rather than inside the micelles. However, with crystalline educts, the surfactant was crucial to help solubilize the reactants in the aqueous medium and enhance the yield of the reaction. This is particularly true for **3i**, **4a**, **4b**, and **4g**, for which 5% of TPGS-750-M was required for optimal yield. To demonstrate the efficacy of our catalytic system and thereby its potential industrial application as a sustainable process, the reaction was next attempted on a multigram scale. Thus, 5 mmol of **1b** and 3-phenylpropylamine (**2**) in TPGS-750-M (2 wt%) successfully led to **3b** in 86% yield under our conditions.

Finally, the kinetic parameters of this reaction were monitored (Figure 5). Firstly, at 50 °C, the reaction with D-glucose as the reducing agent was faster than that with NaAsc. Indeed, after 30 min, 20% conversion was observed (purple), and the

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Figure 5. Kinetics of the reaction at RT and 50 °C with p-glucose and sodium ascorbate. Reaction conditions: $Cu(OTf)_2$ (10 mol%), L1 (20 mol%), reducing agent (10 mol%), NaOtBu (2 equiv.), 3-bromotoluene (1 equiv.), 3-phenylpropylamine (1.2 equiv.), TPGS-750-M (2 wt%), 50 °C or RT. [a] Average yield of two runs. Yields were determined by HPLC with a UV detector and benzophenone as an external standard.

conversion reached 60% after 2 h. In contrast, with NaAsc, a latency time of 4 h was necessary before the formation of **3 b** (orange). It is notable that the conversion rate after this latency time is similar to the rate observed for the reaction with D-glucose. Interestingly, a latency time of 6 h was also observed (green) if the reaction was performed with D-glucose at room temperature. We hypothesized that this period is required to reduce the inactive Cu^{II} species into the active Cu^I species. This induction period might also suggest the formation of nanoparticles as the active catalysts for two reasons:

- (1) A C–N cross-coupling reaction was achieved recently with copper nanoparticles^[22] as a catalyst.
- (2) D-Glucose is an excellent reducing agent for the formation of copper nanoparticles in water.^[23]

However, different experiments performed in our laboratory invalidated this hypothesis (see Supporting Information, pp. S12–S13).

Finally, a reasonable mechanism has been proposed to explain the different observations described in the Supporting Information (see pp. S14–S15). The Cu^I species is generated in situ from the Cu^{II} species and p-glucose. The nucleophilic substitution of the Cu^{II} species by the amine leads to the formation of [Cu^INu] (intermediate **A**). The oxidative addition of the aryl halide to intermediate **A** then generates a transient Cu^{III} species (**B**). Finally, the C–N bond is formed by reductive elimination from **B** to form the target compound and regenerate the initial Cu^{II} species (Scheme 1).

Conclusions

We have developed the first Ullmann-type reaction at low temperature [room temperature (RT) or $50 \,^{\circ}$ C] under micellar conditions for primary aliphatic amines. These mild conditions are



Scheme 1. Proposed mechanism of the copper cross-coupling reaction in the presence of D-glucose.

simple, yet robust and cheap. The use of renewable feedstocks (p-glucose and TPGS-750-M, which is composed of vitamin E), the absence of organic solvent, and the economy of energy make these conditions environmentally friendly and adaptable to industrial production. This easy-to-handle procedure is extremely competitive compared to palladium-based reactions and may be used to synthesize N-containing molecules such as drugs or organic light-emitting diodes (OLEDs).

Experimental Section

General procedure

The amine (1.2 equiv.) and aryl or heteroaryl halide (1 equiv.) were added to an aqueous solution of TPGS-750-M (2 wt%,

1 mLmmol⁻¹). The mixture was degassed with bubbling argon (5 min). NaOtBu (97% purity, 2 equiv.), Cu(OTf)₂ (10%), dipivaloylmethane (20%), and D-glucose (10%) were added, and the resulting mixture was stirred (at 1200 rpm) at RT or 50 °C (20 h). The mixture was extracted twice with ethyl acetate (3 mL). The combined organic layers were evaporated, and the crude residue was purified by silica gel column chromatography with *n*-heptane and ethyl acetate as the eluent.

N-Benzyl-3-methylaniline (3a)

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Compound **3a** was prepared by the general procedure with Cu(OTf)₂ (18.0 mg, 0.050 mmol), dipivaloylmethane (20.9 µL, 0.100 mmol), p-glucose (9.0 mg, 0.050 mmol), 3-bromotoluene (60.6 µL, 0.500 mmol), benzylamine (65.6 µL, 0.600 mmol), and NaOtBu (99 mg, 1.00 mmol) in aqueous TPGS-750-M (2 wt%, 0.50 mL), followed by purification by column chromatography (SiO₂) with *n*-heptane/ethyl acetate (95:5), to yield **3a** as a yellow oil (81 mg, 82%). ¹H NMR (400 MHz, CDCl₃) δ = 2.30 (s, 3 H), 3.90-4.06 (br s, 1H), 4.34 (s, 2H), 6.46–6.59 (m, 3H), 7.09 (t, *J*=7.5 Hz, 1H), 7.27–7.41 ppm (m, 5H); ¹³C NMR (100 MHz, CDCl₃) δ = 21.7, 48.4, 110.0, 113.6, 118.6, 127.2, 127.6, 128.6, 129.2, 139.1, 139.6, 148.3 ppm.

Keywords: amination • amines • carbohydrates • copper • micelles

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Received: June 15, 2016 Published online on ■■ ■, 0000

FULL PAPERS

A spoonful of sugar: A low-temperature Ullmann-type reaction under micellar conditions in water is developed for the coupling of primary aliphatic amines. The use of renewable feedstocks (D-glucose and the surfactant TPGS-750-M, which is composed of vitamin E), the absence of organic solvent, and the economy of energy make these conditions environmentally friendly and adaptable to industrial production.



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D-Glucose: An Efficient Reducing Agent for a Copper(II)-Mediated Arylation of Primary Amines in Water