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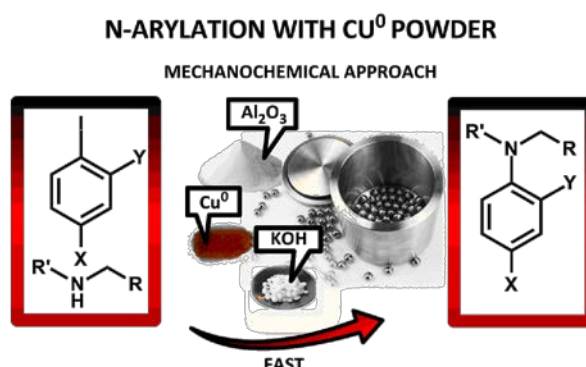
Highly efficient mechanochemical *N*-arylation of amino alcohols and diamines with Cu⁰ powder

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Abstract Cu⁰-catalysed arylations have rightly acquired great importance over the last decade. This paper reports the *N*-arylation of amino alcohols and diamines with iodobenzene derivatives in a planetary ball mill and an investigation into the procedure. This newly developed solvent-free protocol is fast, efficient and occurs under the mechanochemical activation of metallic copper powder. It does not require additional ligands and gives excellent yields. This paper aims to broaden the scope of mechanochemical Cu⁰-activation and so a new one-pot, two-step synthesis that combines CuAAC and *N*-arylation has been successfully performed and reported herein.

Key words *N*-arylation, mechanochemistry, Cu⁰-catalysed cross-coupling, solvent-free reaction; amino alcohols

1. Introduction

Cu⁰-catalysed organic reactions have become very important over the last decade. Copper catalysts are an appealing and cost-effective alternative to palladium. The high demand for Pd and its low natural abundance have prompted a need for alternative, sustainable, Cu-based synthetic protocols.¹ Early investigations were largely focused on the use of stoichiometric organocopper(I) species, such as Gilman reagents,² despite their inherent instability when used in cross-coupling reactions. The utility of Cu-salts in forming C-C bonds is highly successful in many processes, such as the oxidative Heck,³ Sonogashira,⁴ Glaser-Hay,⁵ Castro-Stephens,⁶ and Ullmann couplings.⁷

N-Aryl heterocycles are found in many biologically active compounds. Traditionally, they have been prepared via the nucleophilic aromatic substitution of an activated aryl halide and copper-mediated Ullman coupling.⁸ Harsh conditions, high temperatures and long reaction times have limited the use of the classic Ullmann reaction, while the reaction discovered by Buchwald and Hartwig has provided breakthroughs.⁹ Regardless of the widespread use of Pd-catalysed C-N coupling, recent modifications of the Ullmann coupling have allowed it to

maintain its long-standing position in the synthesis of *N*-arylated heterocycles.¹⁰ Besides the traditional Ullmann reaction, the use of phase-transition-catalyst as an auxiliary and the post-Ullmann reactions using ligands has gained higher applicability.¹¹

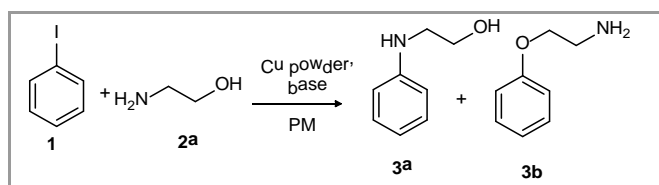
Metallic copper powder is one of the cheapest solid catalysts available, but usually necessitates long reaction times and relatively high temperatures to function.¹² Enabling techniques, such as microwave (MW),¹³ ultrasound (US)¹⁴ and their combined use,¹⁵ mechanochemistry,¹⁶ and flow reactors¹⁷ are the most reliable energy sources with which to activate and exploit metallic catalysts in chemical reactions.¹⁸ In particular, US¹⁹ and ball mills²⁰ have found in metal surface activation one of its primary domains. Since both US and mechanochemical grinding are able to convert mechanical energy into chemical outcomes,²¹ the planetary mill (PM) system can be exploited to activate the copper surface. Our experience has shown that Cu⁰ can provide Cu(I) by means of a mechanically-promoted redox reaction between Cu(0) and the Cu oxide present on the metal surface.²² In fact, Ullman-type reactions commonly involve CuI or CuCl species. The use of PM for metal activation has been well documented,²³ and investigated as a tool with which to reduce the energy demand in C-C couplings²⁴ and is well suited for process intensification and scale up.²⁵

Within a project involving an extensive screening of Cu⁰-catalysed organic reactions, we have focused on the *N*-arylation of amino alcohols and diamines. This interesting reaction was studied by Arai *et al.* in 1977 and observed the higher reactivity of amino alcohols over nucleophilic butyl amine in the presence of a Cu(I) catalyst.²⁶ More recently, Buchwald has described *N*- and *O*-arylations of β -amino alcohols in various solvents and bases.²⁷ Jiao *et al.*²⁸ have already applied Cu⁰ powder to Ullman couplings with methylamine, with prolonged heating (12 hrs) at 100 °C. With the aim of developing a green protocol for ligand- and solvent-free Ullman reactions, we have replaced Cu(I) salts with Cu⁰ powder, reacted in PM with iodobenzene derivatives and amino alcohols. To the best of our knowledge, this is the first

mechanochemical reported procedure for β -amino alcohols *N*-arylation.

2. Results and discussion

Controlling the reaction site and obtaining high N/O selectivity is the major challenge in the arylation of β -amino alcohols. The presence of water and the choice of the base determine N/O reaction selectivity. A preliminary model for *N*-arylation reactions with iodobenzene (**4a**) and ethanolamine (**5a**) was therefore set up (Scheme 1). We decided to perform the reaction in the presence of KOH, as it is known to give high selectivity toward C-N formation.



Scheme 1 Synthetic scheme of *N*-arylation of ethanolamine (**1**) with iodobenzene (**2a**)

The N-C coupling between iodobenzene (1 mmol) and ethanolamine (3 mmol) was carried out in a stainless steel jar (50 mL) with 10 balls (100 mm \varnothing), Cu⁰ powder (1 mmol), KOH (3.4 mmol) and basic aluminium oxide (1 g) as a grinding auxiliary. We added both KOH and basic aluminium oxide to the Cu⁰ powder (1eq) because the combination of these two bases fulfils the dual roles of speeding up reaction conversion and that of a grinding auxiliary. The number of stress events and stress frequency have a significant influence on reaction outcome and are correlated to ball diameter and number.¹⁵ Three different reaction conditions were compared. Ball diameters of 2 mm to 10 were tested, as depicted in Table 1. Small balls were added to the large 10 mm ones to fill the empty spaces and increase the active surface area and ball number was also varied while other parameters were fixed (time = 30 min, rotation speed = 650 rpm, auxiliary = 1 g of Al₂O₃).

We observed that an increase in effective energy transfer to the mill boosted reaction conversion from 77% to 82% in 30 minutes (Entry 1 and 2, Table 1). Our previous experience,²⁰ lead us to a further improvement in a third experiment; overall milling ball mass was kept constant, while ball size and ball number were varied. The yield reached 98% in 30 minutes as a result of the increase in grinding material active surface area.

This study gave good reaction conversion, while observed N/O selectivity was 95/5, which increased slightly when the reaction was performed using smaller balls (entry 3, Table 2).

Table 1 Screening of ball features

Entry	Balls Number			Active surface Area ^a (mm ²)	Yield 3a (Conv.)	N/O select.
	\varnothing = 2 mm	\varnothing = 5 mm	\varnothing = 10 mm			
1	-	-	10	10666	75 (77)	95/5
2	625	-	10	18520	70 (82)	95/5
3	1500	48	-	30144	98 (99)	98/2

^a Active surface area = surface balls + surface jar

The bases that are commonly used for this reaction are salts of alkaline or alkaline-earth metals. The addition of bases is thought to facilitate the otherwise slow nucleophile deprotonation/coordination. Therefore, a set of reactions was performed with the aim of better understanding the effect of the base and grinding auxiliary on the model reaction. Table 2 provides the reaction yields and N/O selectivity. We observed that the reaction is slower in the absence of a base and Al₂O₃ while only starting material was recovered in the presence of base and silica.

Table 2 Influence of the base and grinding auxiliary on the reaction yield

Entry	Base	Grinding Auxiliary	Yield 3a (Conv.)	N/O selectivity
1	KOH	Al ₂ O ₃	98	98/2
2	none	none	67	96/4
3	KOH	Silica	-	-

Reaction conditions: iodobenzene (1 mmol), ethanolamine (3 mmol), Cu⁰ powder (1 mmol), KOH (3.4 mmol), Al₂O₃ (1 g), in a stainless steel jar (50 mL) with 1500 balls (\varnothing =2 mm) and 48 balls (\varnothing =5 mm) at 650 rpm.

Different experimental conditions have been compared in a study of the efficacy of mechanochemistry on the Cu⁰ powder-catalysed Ullman-type reactions. Ball mill activation²⁹ is compared to US promotion³⁰ and for the sake of comparison, the reaction was left at room temperature under conventional stirring³¹. As depicted in Figure 1, all reactions were performed at room temperature and the molar ratio used in the optimized model reaction was kept. A cup-horn reactor was used when the reaction was performed under sonochemical conditions (R.E.U.S., Contes, France). Fig. 1 provides an overview of the time-dependent yield. As already mentioned, full conversion was obtained in 30 minutes in the planetary ball mill, while the reaction ends after 3 hrs. Under conventional conditions, 35% conversion was reached after 2 days of agitation.

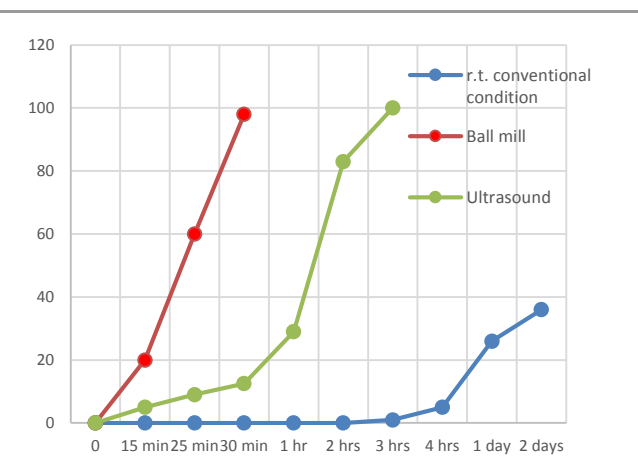
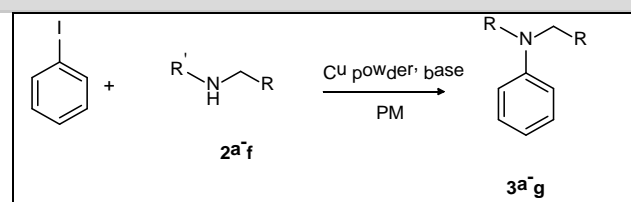


Figure 1 Yield of the solvent free Cu⁰ catalysed Ullman-type reaction. Reaction conditions: iodobenzene (1 mmol), ethanolamine (3 mmol), Cu⁰ powder (1 mmol), KOH (3.4 mmol).

As already proved by Ma *et al.*, amino alcohol structural features may contribute to the formation of a copper chelating intermediate,³² which makes the aromatic position more electrophilic and susceptible to substitution, while bringing the amine closer to the attack position and accelerating the reaction

rate. Based on this knowledge we observed that under mechanochemical activation alkyl amines were unreactive and only starting material was isolated starting from iodobenzene and a set of four different primary amines (propylamine, propargylamine, benzylamine, octylamine). On the basis of these results our optimized procedure was tested over a set of different amino alcohols and diamines. As depicted in Table 3, from the comparison of different aminoalcohols we observed that the highest yield were obtained in presence of aminoethanol while only a slight decrease of the yield was observed when 3-aminopropanol was used (Table 3, entry 2). No trace of desired product was found in presence of 6-aminoheptan-1-ol (Table 3, entry 3). The reaction showed good tolerance to secondary alcohols and 3-amino-2-propanol reacted to obtain the product **3g** in 85 % yield, while only traces of the final product were obtained with the *O*-methyl ether of ethanolamine (Table 3, entries 5 and 6).

Table 3 Screening of the mechanochemical *N*-arylation of different amines with iodobenzene

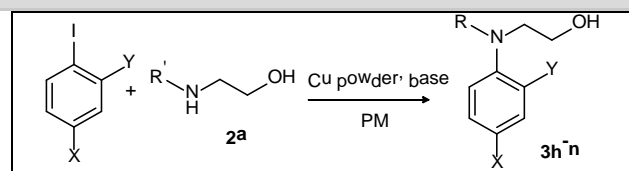


Entry	Amine	Product	Yield (%) ^a
1			98 (99)
2			92 (95)
3			- (-)
4			99 (>99) ^b
5			- (3)
6			85 (89)

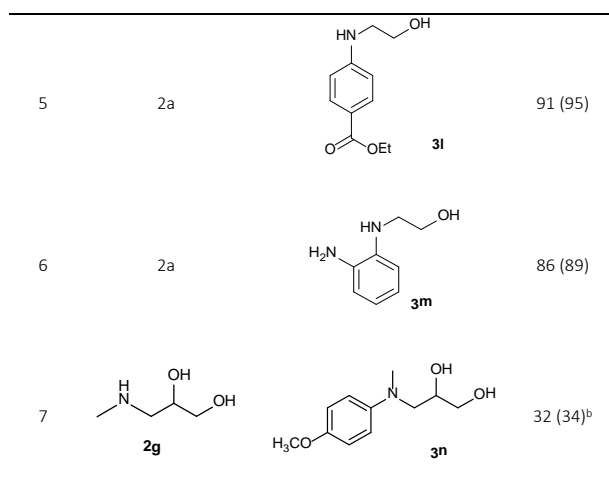
Reaction Conditions: 1 mmol iodobenzene derivatives, 3 mmol **2a-f**, 1 mmol Cu⁰ powder, 3.4 mmol KOH, 1 g Al₂O₃, 30 min, 650 rpm; Stainless steel jar (50 mL), 1500 small balls and 48 medium balls. ^a Determined by GC-MS. ^b The reaction was carried out with 10 mmol **2d**, 15 min, 650 rpm.

Different iodobenzene derivatives were also screened (see Table 4). The methodology was proved to be compatible with many different functional groups and it is worth noting that the ketone (Table 4, entry 4) and esters (Table 4, entry 5) groups did not react with the amine. The literature has shown that the reactivity of aryl halides is greatly improved by electron-withdrawing groups, such as -NO₂, -COR, -COOR, -Br, and limited by electron donating groups, such as -OR, -NH₂, when the reaction was conducted in solution.³³ In our case, these “guidelines” were not respected; the reactions with 4-iodoanisole (Table 4, entry 1) and 2-iodoaniline (Table 4, entry 6) worked surprisingly well, whereas it was necessary to carry out the 4-iodonitrobenzene reaction for 4 hrs without the base (Table 4, entry 2). These results indicate whether the mechanism of this reaction may be related to the one proposed by Ma *et al.* in which the cuprous chelate coordinates the aryl halides to provide the π -complex.³² When the nitro group is present as a substituent, it draws electron density from the benzene by resonance and inductive effects and changes the nature of the chelating intermediate. The procedure was also tested with *N*-methyl isoserinol (Table 4, entry 7)³⁴ a versatile and useful building block for organic medicinal chemistry. The reaction showed high selectivity towards the amino group (70/1 N/OH selectivity) and the product was obtained in 32 % yield.

Table 4 Screening of the mechanochemical *N*-arylation of ethanolamine with different iodobenzene derivatives

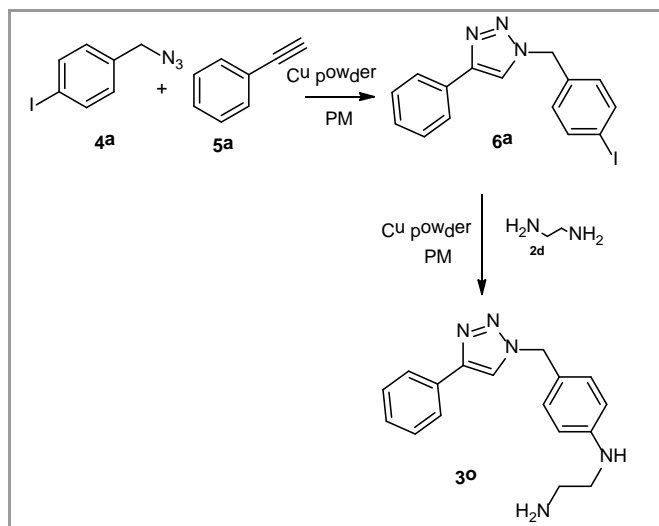


Entry	Amine	Product	Yield (%) ^a
1			96 (98)
2e			81 (85) ^b
3			96 (99)
4			87 (92)



Reaction Conditions: 1 mmol iodobenzene derivatives, 3 mmol **2a-g**, 1 mmol Cu⁰ powder, 3.4 mmol KOH, 1 g Al₂O₃, 30 min, 650 rpm; Stainless steel jar (50 mL), 1500 small balls and 48 medium balls. ^a Determined by GC-MS. ^b The reaction was carried out without KOH and Al₂O₃ in 4h.

Finally to broad the scope of this study, on the basis of our previous experience on CuAAC under mechanochemistry activation, we explored a sequential one-pot/two steps synthesis in PM. A new mechanochemical methodology based on a sequence of CuAAC click reaction followed by an *N*-arylation reaction was designed and performed with the aim to fulfill green chemistry principles (Scheme 2). *p*-Iodobenzyl azide and phenylacetylene were reacted to obtain 1-(4-iodobenzyl)-4-phenyl-1H-1,2,3-triazole (**6a**), which was used for Ullman *N*-arylation with ethylenediamine (**2d**) without any further purification. The synthetic scheme afforded to product **3o**³⁵ in 56% yield.



Scheme 2 One-pot two step mechanochemical reactions (Reaction conditions for step 1: 1 mmol **4a**, 1 mmol **5a**, 1 mmol Cu⁰ powder, 10 min, 650 rpm; for step 2: 10 mmol of **2d**, 2 h, 650 rpm. All reactions were performed in a stainless steel jar (50 mL), 1500 small balls and 48 medium balls)

3. Conclusions

In conclusion, we have developed a simple and easily carried out method that makes use of a convenient, cost effective, environmentally friendly Cu⁰ powder catalyst. The ball milling reactions were proved to be efficient and afforded the products

in short reaction times at high yields, which are also due to the easy work-up. The *N*-arylation PM reaction has been set-up and various functional groups tested, demonstrating the high versatility of the method. Furthermore, high conversions, short reaction times and easy work-up have all been obtained in this procedure. Acceptable yields have been achieved from a new mechanochemical one pot/two steps methodology based on a sequence of CuAAC click reaction followed by an *N*-arylation reaction.

Acknowledgment

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

References and Notes

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- (29) **General Procedure for Cu⁰-catalyzed N-arylation of amino alcohols or ethylenediamine with iodobenzenes in ball mill:** the milling jar (50 mL; stainless steel) were equipped with 1500 milling balls (d = 2 mm, stainless steel) and 48 medium balls (d = 5 mm, stainless steel). Afterwards basic Al₂O₃ 90 active (1 g), KOH (3.7 mmol) were added and milled for 10 min at 450 rpm. After that the aryl iodide (1 mmol), the amino alcohol (3 mmol) or ethylenediamine (10 mmol) and Cu⁰ powder (1 mmol, 63 mg) were added in the given order. Milling was accomplished at 650 rpm for 30 min. After cooling of the milling jar to room temperature, the crude products were washed from Al₂O₃ on Büchner funnel with a sintered glass disc using diethyl acetate. The solvent was evaporated in vacuum, the crude products were dried and analyzed by GC-MS. The mixture was purified by flash chromatography on silica gel (hexane:ethylacetate) to afford the desired product. The pure products were analyzed by ¹H, ¹³C NMR spectroscopy and MALDI-TOF mass spectrometry after dissolution in an appropriate solvent.
- (30) When performed under sonochemical conditions, the reaction mixture was reacted in a ultrasonic bath equipped with a transducer operating at 25 KHz. (24 KHz, R.E.U.S. Contes, France)
- (31) When performed under conventional condition the reaction was stirred at room temperature.
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- (34) 3-(*N*-methyl-4-methoxyphenylamino)propane-1,2-diol **3n**: yellowish amorphous solid (32%). ¹H NMR (300 MHz, CDCl₃): δ 6.85 (4 H, m), 3.95 (1 H, m), 3.76 (4 H, m), 3.58-3.52 (1H, dd, J = 6 Hz), 3.29-3.26 (1 H, m), 3.16 (1 H, m), 2.87 (3 H, s) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 153.28, 144.64, 116.69, 114.57, 68.89, 64.20, 57.78, 55.62, 40.51 ppm. m/z (MALDI-TOF MS): calcd for C₁₁H₁₇N₃O₃ [M + H]⁺: 212.1256, found: 212.1264.
- (35) Triazole derivative **3o**: white powder (56%). ¹H NMR (300 MHz, CDCl₃): δ 7.71 (2 H, d, J = 8.4 Hz), 7.53 (1 H, s), 7.34 (2 H, d, J = 7.3 Hz), 7.27-7.17 (1H, m), 6.56 (2 H, d, J = 8.5 Hz), 5.36 (2 H, s), 3.11 (2 H, br s), 2.89 (2 H, t, J = 5.7 Hz) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 149.3, 148.3, 131.1, 130.2, 129.2, 128.4, 126.1, 123.1, 119.6, 113.5, 54.5, 46.6, 41.4 ppm. m/z (MALDI-TOF MS): calcd for C₁₇H₁₉N₅ [M + H]⁺: 294.1640, found: 294.1644.