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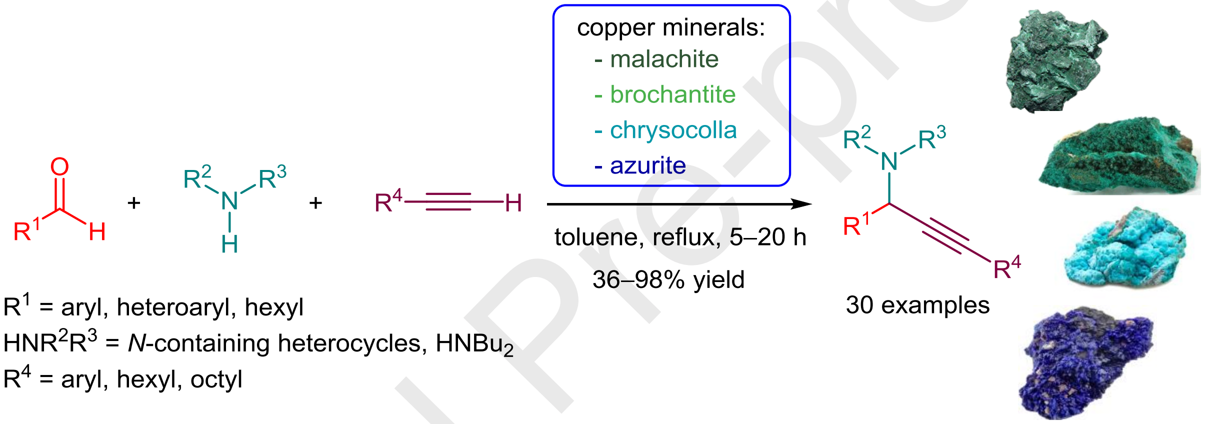
GRAPHICAL ABSTRACT



ABSTRACT

The highly atom efficient three-component reaction of aldehydes, secondary amines and acetylenes to form propargylamines (A^3-coupling) has been studied with twelve readily available copper-containing minerals. It was found that the reaction could easily be performed in the presence of malachite, brochantite, chrysocolla and azurite in toluene at reflux. The desired products were obtained in good to excellent yields.

KEYWORDS

Copper-containing minerals, Catalysis, A^3-coupling, Multicomponent reaction

Introduction

Propargylamines are valuable intermediates and have found broad applications in organic synthesis for the construction of various nitrogen-containing heterocycles [1,2]. Moreover, the propargylamine moiety can be found in commercially available drugs: rasagiline and deprenyl are irreversible inhibitors of the monoamine oxidase-B (MAO-B) enzyme and are used for the treatment of Parkinson's disease and Alzheimer's disease [3–6], while racemic oxybutynin is a muscarine receptor antagonist drug which was developed for the treatment of overactive bladder [7,8] (Fig. 1). Therefore, the synthesis of this type of compounds has attracted considerable attention.

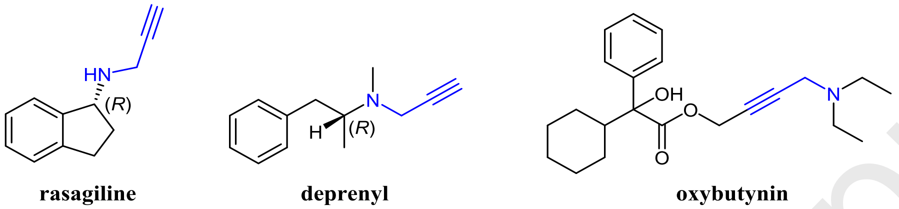
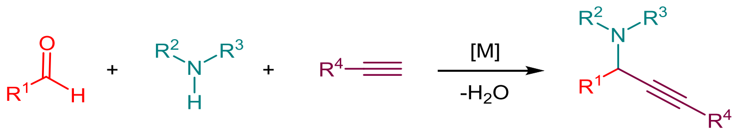


Figure 1. Marketed drugs containing a propargylamine structural unit.

The classical method for the assembly of propargylamines is based on the nucleophilic addition of a metal acetylide, formed by the reaction of the corresponding acetylene derivative with an organometallic reagent, to an imine. The disadvantages of this traditional process are the use of an equimolar amount of an expensive and moisture-sensitive organometallic reagent [9–11]. About two decades ago, Li and Wei described an efficient CuBr-$RuCl_3$-catalyzed reaction of an aldehyde, an amine and an alkyne (also known as A^3-coupling) for the preparation of propargylamines (Scheme 1), where the transition metal catalyst was only applied in a catalytic amount (30 mol% CuBr and 3 mol% $RuCl_3$) [12]. Subsequently, several modifications of this three-component reaction have been developed [1]. In general, the A^3-coupling is catalyzed by salts and complexes of transition metals, such as copper, silver, gold, iron, indium, iridium, mercury, manganese, nickel, cobalt, zirconium, bismuth and rhenium [13–15]. Among these, copper-catalyzed A^3-coupling reactions have been the most investigated, with catalysts ranging from Cu(0) nanoparticles [16], and simple Cu(I) or Cu(II) halogenides to special copper-containing complexes [17].



Scheme 1. Transition metal-catalyzed A^3-coupling protocol.

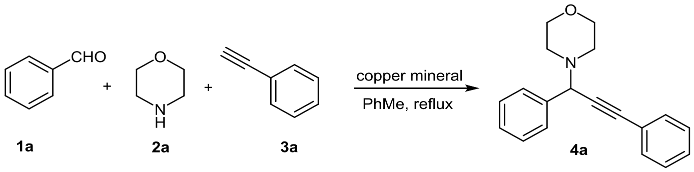
Naturally occurring clays or their modified forms are widely used to catalyse various types of organic reactions [18,19]. Both elemental copper and synthetic copper salts have long been known as catalysts in a number of organic transformations, for example C–H bond functionalizations [20,21], aerobic oxidations of organic molecules [22], azide–alkyne 1,3-dipolar cycloadditions [23] and cross-coupling reactions [24–26]. Yu and co-workers reported [3+3] cycloadditions of C,N-cyclic azomethine imines catalyzed by basic copper carbonate [$Cu_2CO_3(OH)_2$]; however, the origin of the latter was not disclosed by the authors [27]. It is also noteworthy that calcination of naturally occurring copper-containing minerals (malachite, rosasite, aurichalcite) can be applied for the manufacturing of synthetic copper-containing catalysts, notably silica-nanosphere-embedded copper oxide and graphene oxide-supported copper oxide [28–33]. Nevertheless, to the best of our knowledge, the catalytic role of naturally occurring copper ores has not been studied in organic synthesis.

Herein, we report an A^3-coupling reaction catalyzed by readily available copper-containing minerals. The direct use of minerals in their native form makes their transformation into synthetic copper compounds unnecessary, thereby rendering this approach environmentally friendly.

Results and Discussion

Based on literature data [34,35], the first experiments were conducted in toluene at reflux using benzaldehyde (**1a**, 2.0 mmol), morpholine (**2a**, 2.0 mmol, 1.0 eq) and phenylacetylene (**3a**, 2.4 mmol, 1.2 eq, Table 1). The reaction time was 2.5 h and the amount of various powdered copper-containing minerals used was 40 mg (*ca*. 4.1–25 mol%, depending on the catalyst). Sulfide minerals were found to be ineffective in this A^3-coupling reaction (Table 1, entries 1–5). Among copper silicates, the catalytic effect of dioptase and chrysocolla was studied. With dioptase, product **4a** was isolated in 72% yield (Entry 6). In the case of chrysocolla, an even higher yield (86%) was observed (Entry 7). The outcome of the reaction was practically identical when brochantite, a copper sulfate-type mineral was used (Entry 8). Next, the activity of copper carbonate minerals, including aurichalcite, rosasite, malachite and azurite was investigated (Entries 9–12). Whereas aurichalcite (Entry 9) and rosasite (Entry 10) proceeded in an unsatisfactory manner, malachite and azurite were found to be equally efficient when compared with brochantite and chrysocolla (Entries 11, 12). Malachite is one of the most important, inexpensive and abundant copper ores, therefore further optimization of the model reaction was performed with this mineral.

Table 1. Optimization of the reaction conditions.[a]



Entry	Copper-containing mineral	Quantity of catalyst (mg)	Time (h)	Yield 4a (%)[b]
1	covellit (CuS)	40	2.5	0
2	chalcocite (Cu_2S)	40	2.5	1
3	chalcopyrite ($CuFeS_2$)	40	2.5	0
4	bornite (Cu_5FeS_4)	40	2.5	0
5	bournonite ($PbCuSbS_3$)	40	2.5	0
6	dioptase ($Cu_6Si_6O_{18} \cdot 6\ H_2O$)	40	2.5	72
7	chrysocolla [$(Cu,Al)_2H_2Si_2O_5(OH)_4 \cdot n\ H_2O$]	40	2.5	86
8	brochantite [$Cu_4(SO_4)(OH)_6$]	40	2.5	80
9	aurichalcite [$(Zn,Cu)_5(CO_3)_2(OH)_6$]	40	2.5	22
10	rosasite [$(Cu,Zn)_2(CO_3)(OH)_2$]	40	2.5	32
11	malachite [$Cu_2(CO_3)(OH)_2$]	40	2.5	83
12	azurite [$Cu_3(CO_3)_2(OH)_2$]	40	2.5	80
13	malachite	60	2.5	79
14	malachite	20	2.5	81
15	malachite	10	2.5	80
16	malachite	5	2.5	80
17	malachite	1	2.5	80
18	malachite	5	5	93
19	malachite	5	20	94
20	-	-	20	0

[a] Reagents and conditions: **1a** (2.0 mmol), **2a** (2.0 mmol), **3a** (2.4 mmol), toluene (10 mL), copper-containing mineral, reflux. [b] Isolated yield based on benzaldehyde and morpholine.

In addition to toluene, other solvents including acetonitrile, methanol, water, 2-methyltetrahydrofuran and 2,2,2-trifluoroethanol were examined at reflux for 2.5 h in the presence of 40 mg malachite. However, in these solvents product **4a** could only be detected in trace amounts by HPLC-MS (results not shown in Table 1). When using solvent-free conditions (110 °C, 2.5 h) in the presence of malachite, propargylamine **4a** was obtained in 63% yield (result not shown in Table 1).

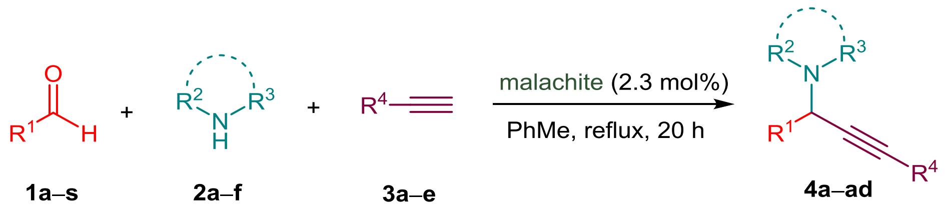
Next, the effect of the amount of catalyst and reaction time was tested. Increasing the amount of malachite from 40 mg to 60 mg did not afford better results (Table 1, entry 13). When reducing the amount of malachite gradually to 1 mg, product **4a** was still obtained in good yield (Entries 14–17);

thus, the catalyst was also effective in very small amounts (down to *ca*. 0.45 mol%, calculated for the Cu ion). Nevertheless, for practical reasons, 5 mg of malachite was employed in further investigations. Increasing the reaction time from 2.5 h to 5 h or 20 h led to higher yields (93% and 94%, respectively; entries 18, 19).

It is also noteworthy that no product (**4a**) was detected in the control experiment in the absence of catalyst (Table 1, entry 20). The presumed role of the catalyst is to form a copper acetylide in the first step that reacts with the iminium ion, leading to the formation of the targeted propargylamine, as suggested by Van der Eycken and co-workers [1].

Although in our model reaction (with **1a**, **2a** and **3a**) 2.5 hours were sufficient to produce the product (**4a**) in good yield, other substrates led to slower conversions, therefore we considered 20 hours as the optimal reaction time. With the optimized conditions in hand, we explored the substrate scope of this three-component condensation (Table 2). First, the reaction of benzaldehydes with varied substitution patterns (**1b**–**i**) with morpholine (**2a**) and phenylacetylene (**3a**) was tested. Aldehydes with either electron-withdrawing or electron-donating groups attached to the benzene ring (**1b**–**i**) were suitable substrates and provided the corresponding products (**4b**–**i**) in good yields (Table 2, entries 2–9). The reaction of bulkier naphthalene-2-carbaldehyde (**1j**) and 9*H*-fluorene-2-carbaldehyde (**1k**) also proceeded smoothly to afford the desired products (**4j** and **4k**) in 91% and 87% yields, respectively (Entries 10, 11). The use of heteroaromatic carbaldehydes bearing a thiophenyl, furanyl, thiazolyl or pyridinyl moiety was also successful to give products **4l**–**p** (Entries 12–16). Lower yields were obtained when 5-fluoro-1-benzothiophene-2-carbaldehyde (**1q**) and 1-methylpyrrol-2-carboxaldehyde (**1r**) were employed (Entries 17, 18). The reaction was also successfully extended to the aliphatic aldehyde heptanal which gave propargylamine derivative **4s** in 88% yield (Entry 19).

Table 2. Study of the substrate scope for the A^3-coupling.[a]



Entry	1	R^1	2	R^{2}R^3	3	R^4	Yield 4 (%)
1	**a**	Ph	**a**	$-(CH_2)_2O(CH_2)_2-$	**a**	Ph	94/87[b]/89[c]/94[d] (**4a**)
2	**b**	2-$F_3CC_6H_4$	**a**	$-(CH_2)_2O(CH_2)_2-$	**a**	Ph	84/76[e] (**4b**)
3	**c**	3-BrC_6H_4	**a**	$-(CH_2)_2O(CH_2)_2-$	**a**	Ph	91/79[e] (**4c**)
4	**d**	4-$F_3CC_6H_4$	**a**	$-(CH_2)_2O(CH_2)_2-$	**a**	Ph	85 (**4d**)
5	**e**	4-NCC_6H_4	**a**	$-(CH_2)_2O(CH_2)_2-$	**a**	Ph	65 (**4e**)
6	**f**	4-*i*-PrC_6H_4	**a**	$-(CH_2)_2O(CH_2)_2-$	**a**	Ph	76 (**4f**)
7	**g**	4-$MeOC_6H_4$	**a**	$-(CH_2)_2O(CH_2)_2-$	**a**	Ph	83/21[e] (**4g**)
8	**h**	4-$PhOC_6H_4$	**a**	$-(CH_2)_2O(CH_2)_2-$	**a**	Ph	92/92[d] (**4h**)
9	**i**	2,3-diF-C_6H_3	**a**	$-(CH_2)_2O(CH_2)_2-$	**a**	Ph	81 (**4i**)
10	**j**	naphthalen-2-yl	**a**	$-(CH_2)_2O(CH_2)_2-$	**a**	Ph	91 (**4j**)
11	**k**	9*H*-fluoren-2-yl	**a**	$-(CH_2)_2O(CH_2)_2-$	**a**	Ph	87 (**4k**)
12	**l**	thiophen-2-yl	**a**	$-(CH_2)_2O(CH_2)_2-$	**a**	Ph	80 (**4l**)
13	**m**	thiophen-3-yl	**a**	$-(CH_2)_2O(CH_2)_2-$	**a**	Ph	78 (**4m**)
14	**n**	5-methylfuran-2-yl	**a**	$-(CH_2)_2O(CH_2)_2-$	**a**	Ph	85 (**4n**)
15	**o**	1,3-thiazol-4-yl	**a**	$-(CH_2)_2O(CH_2)_2-$	**a**	Ph	94 (**4o**)
16	**p**	pyridin-3-yl	**a**	$-(CH_2)_2O(CH_2)_2-$	**a**	Ph	92 (**4p**)
17	**q**	5-F-benzothiophen-3-yl	**a**	$-(CH_2)_2O(CH_2)_2-$	**a**	Ph	51 (**4q**)
18	**r**	1-Me-1*H*-pyrrol-2-yl	**a**	$-(CH_2)_2O(CH_2)_2-$	**a**	Ph	36 (**4r**)
19	**s**	hexyl	**a**	$-(CH_2)_2O(CH_2)_2-$	**a**	Ph	88 (**4s**)
20	**a**	Ph	**a**	$-(CH_2)_2O(CH_2)_2-$	**b**	4-MeC_6H_4	93 (**4t**)
21	**a**	Ph	**a**	$-(CH_2)_2O(CH_2)_2-$	**c**	4-$O_2NC_6H_4$	47 (**4u**)
22	**a**	Ph	**a**	$-(CH_2)_2O(CH_2)_2-$	**d**	hexyl	83 (**4v**)
23	**a**	Ph	**a**	$-(CH_2)_2O(CH_2)_2-$	**e**	octyl	77 (**4w**)
24	**a**	Ph	**b**	$-(CH_2)_4-$	**a**	Ph	59 (**4x**)
25	**a**	Ph	**c**	$-(CH_2)_5-$	**a**	Ph	95 (**4y**)
26	**o**	1,3-thiazol-4-yl	**c**	$-(CH_2)_5-$	**a**	Ph	67 (**4z**)
27	**a**	Ph	**d**	$-(CH_2)_6-$	**a**	Ph	87 (**4aa**)
28	**a**	Ph	**e**	$-(CH_2)_2NMe(CH_2)_2-$	**a**	Ph	96/88[b]/92[c]/98[d] (**4ab**)
29	**o**	1,3-thiazol-4-yl	**e**	$-(CH_2)_2NMe(CH_2)_2-$	**a**	Ph	89 (**4ac**)
30	**a**	Ph	**f**	Bu[f]	**a**	Ph	71 (**4ad**)

[a] Reagents and conditions: **1** (2.0 mmol), **2** (2.0 mmol), **3** (2.4 mmol), malachite (5 mg), PhMe (10 mL), reflux, 20 h. [b] Azurite (5 mg) was used. [c] Brochantite (5 mg) was used. [d] Chrysocolla (5 mg) was used. [e] The reaction time was 5 h. [f] Dibutylamine was used.

Subsequently, the reaction of 4-substituted phenylacetylenes with benzaldehyde (**1a**) and morpholine (**2a**) was investigated. 4-Methylphenylacetylene (**3b**) showed good reactivity giving product **4t** in 93% yield (Entry 20). However, 4-nitrophenylacetylene (**3c**) containing a strongly electron-withdrawing group produced the desired propargylamine (**4u**) only with a moderate yield of 47% (Entry 21). In addition, the reaction could be performed with aliphatic acetylenes, oct-1-yne (**3d**) and dec-1-yne (**3e**), giving the desired products **4v** and **4w** in 83% and 77% yield, respectively (Entries 22, 23).

To further examine the scope of this three-component reaction, several other secondary amines were tested, in addition to morpholine. Pyrrolidine (**2b**), piperidine (**2c**), hexamethyleneimine (**2d**) and 1-methylpiperazine (**2e**) were also well tolerated, and the products (**4x**–**ac**) were obtained in 59–96% yield (Entries 24–29). Dibutylamine (**2f**), an acyclic secondary amine, was also reacted with benzaldehyde (**1a**) and phenylacetylene (**3a**) to give product **4ad** (Entry 30). An attempted extension of the reaction to aniline as an aromatic amine, with benzaldehyde (**1a**) and phenylacetylene (**3a**), led to Schiff-base formation, but no further reaction with **3a** took place under the applied conditions. Among the target compounds described in Table 2, **4a**,**c–g**,**j**,**l**,**m**,**s–y**,**aa**,**ab**,**ad** are known in the literature (see references in the ESI), while **4b**,**h**,**i**,**k**,**n–r**,**z**,**ac** are new compounds.

In addition to malachite, the three-component reaction of various substrates was also successfully performed in the presence of azurite (Entries 1, 28), brochantite (Entries 1, 28) or chrysocolla (Entries 1, 8, 28) under the optimized conditions, and the expected products (**4a**, **4h**, **4ab**) were isolated in high yields.

Besides its green characteristics, low cost and high abundance [36–38], a further advantage of malachite is its thermal stability. According to our observations, no degradation takes place, and it does not lose its catalytic activity when heated at reflux in toluene. When malachite was kept at 110 °C for 20 h, and the reagents (**1a**, **2a**, **3a**) were added afterwards, the reaction time and yield of **4a** remained practically unchanged. This is in line with the reported thermogravimetric analysis indicating that malachite only begins to degrade at a temperature as high as 250 °C with the loss of water [39].

The malachite catalyzed A^3-coupling reaction of benzaldehyde (**1a**), morpholine (**2a**) and phenylacetylene (**3a**) was further optimized. A detailed summary of the experimental results obtained with an equimolar amount of phenylacetylene, reduced quantity of toluene and malachite, reaction on 20 mmol scale, or distillation instead of chromatography can be found in the ESI.

Attempted filtration and recovery of the catalyst were not successful due to its partial dissolution in the reaction mixture and to the colloidic character of the solid residue. Nevertheless, the procedure described here remains highly economical thanks to the ready availability of malachite and the remarkably low amount used.

Conclusion

In summary, the A^3 multicomponent reaction of aromatic and aliphatic aldehydes, various secondary amines and acetylenes was examined in the presence of commercially available copper-containing minerals in their natural form. The best catalytic effect was obtained with brochantite, malachite, azurite and chrysocolla. The optimization and extension of this novel and highly economical A^3-reaction were studied in detail with malachite, an inexpensive and naturally abundant mineral. Thus, a number of propargylamine derivatives were prepared in good yields in a green procedure. Investigation of other organic reactions catalyzed by copper-containing minerals is currently in progress in our laboratory.

Appendix A. Supplementary data

Supplementary data to this article can be found online at

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- Application of copper-containing mineral catalysts in organic synthesis
- A novel strategy in the field of Cu-catalyzed organic reactions
- Efficient synthesis of propargylamines