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Unconventional Gold-Catalyzed One-Pot/Multicomponent Synthesis of Propargylamines Starting from Benzyl Alcohols

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Abstract: A formal homogeneous gold-catalyzed A^3-coupling, starting from benzyl alcohols, is reported for the straightforward synthesis of propargylamines. This is the first process where these highly valuable compounds have been synthesized, starting from the corresponding alcohols in a one-pot oxidation procedure using MnO_2, followed by a $HAuCl_4 \cdot 3H_2O$ catalyzed multicomponent reaction. The final products are obtained with very good yields in short reaction times, which is of fundamental interest for the synthesis of pharmaceuticals. The usefulness and efficiency of our methodology is successfully compared against the same reaction starting from aldehydes.

Keywords: benzyl alcohols; gold; multicomponent; one-pot; propargylamine

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1. Introduction

Nowadays, organic synthesis is more focused on both efficiency and environmental sustainability due to increasing concern about the prevention of pollution and waste minimization, as the main aims of Green Chemistry. Among the number of developed processes, one-pot procedures [1–4] and multicomponent reactions (MCR) [5–7] are at the forefront of these green and eco-friendly approaches. In the last decade, these protocols have been the center of great attention, especially in the pharmaceutical industry, because of the easy formation of large libraries of organic compounds with biological activities [8–11]. These processes are interesting due to the necessity of a single reaction vessel, while minimizing chemical waste, saving time, solvents and energy, and simplifying practical aspects.

The oxidation of primary alcohols is one of the main reactions in organic synthesis to directly obtain aldehydes [12]. Many organic reactions start from aldehydes and some of them lead to products of biological interest. However, the direct use of different aldehydes could be considered sometimes somewhat toxic, more expensive and overall, more difficult to handle and work with. Moreover, we realized that when using aldehydes, the catalytic traces of acid contained in these reagents could negatively affect the results of the processes (yield and/or enantioselectivity), which might inhibit the catalyst performance [13]. In this field, we pioneered one of the scarce approaches where the in situ-generated aldehyde was further used in an ulterior organocatalytic reaction [14]. It is remarkable that although there exist different protocols for the oxidation of alcohols, the subsequent use of the carbonyl group generated in the oxidation step in a cascade catalytic process is rarer [15–19]. We envisaged that the catalytic reactions starting from the corresponding alcohol would be more convenient than those starting from aldehydes, mainly due to the higher availability and easy handling of the former. Additionally, it is interesting for the final outcome of the reaction, since sometimes the high reactivity of the aldehyde could interfere in other aspects of the multi-step synthesis.

Among the plethora of reactions in the literature that start from an aldehyde, the three-component A^3-coupling for the synthesis of propargylamines and catalyzed by a transition metal between an aldehyde, an alkyne and an amine is of great relevance [20–26]. This approach is the focus of continued interest and has been established as a general route for the construction of nitrogen-containing compounds, giving rise to appealing scaffolds with interesting biological properties (Figure 1). It is remarkable the presence of propargylamine cores in compounds such as Pargyline **I**, a biological active compound involved in the inhibition of MAO-B (Monoamine Oxidase B) and used against neurodegenerative diseases such as Parkinson's or Alzheimer's [27,28]. DPC 961 **II** is also an interesting active compound, used as a second-generation NNRTI (non-nucleoside reverse transcriptase inhibitors) drug with enhanced activity compared to Efavirenz, the treatment of human immunodeficiency virus (HIV) infection [29–31]. Moreover, 1,2,3,4-tetrahydroisoquinoline alkaloids **III** and **IV** are interesting natural products also obtained after a propargylamine intermediate [25].

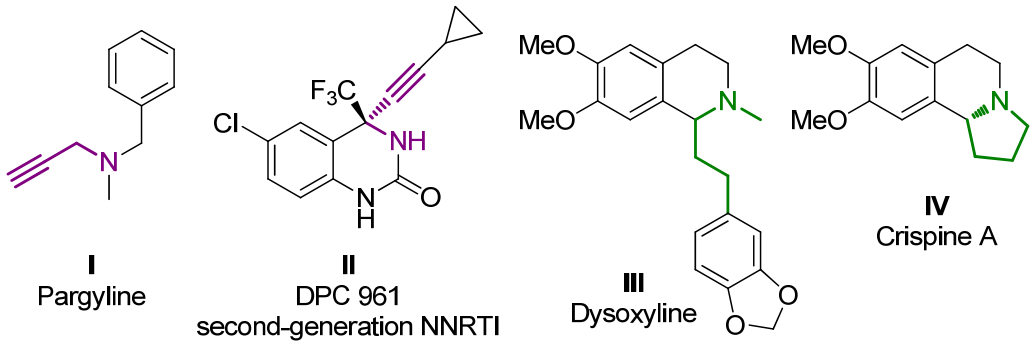
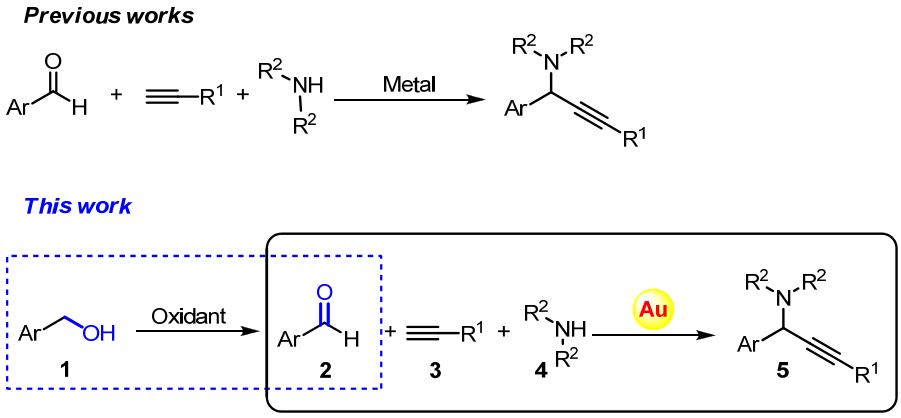


Figure 1. Biologically active propargylamines and natural amines derived from propargylamines.

On the other hand, in the last two decades, the chemistry of gold as a catalyst has emerged as a powerful tool to promote numerous organic transformations [32–43]. It is worth noting that the use of gold catalysts, in homogeneous catalysis, for the preparation of propargylamines has been reported so far [44–55]. There are also pivotal examples of the use of gold nanoparticles in heterogeneous catalysis [56–67]. Due to the importance of the propargylamine structural cores, the development of new more straightforward and sustainable methodologies for building these skeletons is still of great interest. During the preparation of this work, Hwang's group reported the pioneering preparation of propargylamines by a visible-light-mediated copper-catalyzed photoredox hydrogen-atom transfer process [68]. The process was developed using CuCl (5 mol%) and benzoquinone (1.2 equiv.) at room temperature with blue LEDS (light-emitting diodes) and after, up to 24 h. Later on, Shahverdizadeh's group reported the use of silica-encapsulated gold nanoparticles as a nano-reactor for aerobic oxidation of benzyl alcohols and heterogeneous tandem preparation of final propargylamines [69]. It is also remarkable the work pioneered by Dabiri's group in 2014 in a similar reaction, using gold nanoparticles supported on graphene oxide with ionic liquid framework (Au@GO-IL) using high temperature (100 °C) and water as a solvent [70]. However, and to the best of our knowledge, the method reported here is the simplest one to synthesize propargylamines starting from an alcohol and with commercially available oxidant and catalyst. Therefore, this work could represent a crucial precedent of this undeveloped approach (Scheme 1).



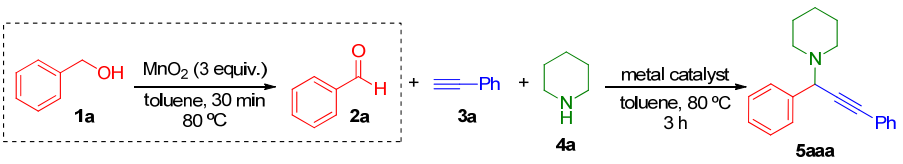
Scheme 1. Hypothesis of work for a A^3-coupling reaction starting from benzyl alcohols.

2. Results and Discussion

Focused on our previous work [14] and analyzing many different oxidants reported in the literature, we chose activated manganese dioxide, MnO_2, as the mildest oxidant and as the most selective and efficient one to straightforward obtain the corresponding aldehydes [71].

We started with a selection of representative and accessible metallic salts (Table 1, entries 1–5). Interestingly, all catalysts assayed were able to promote the catalytic reaction, adding all the reagents in a one-pot/multicomponent procedure, without the necessity of isolating the *in situ*-generated aldehyde **2a**. Remarkably, the gold derivative afforded a total conversion of the process after 2 h of reaction, with a 5 mol% of catalyst and with better results in comparison with the other tested species (Table 1, entry 1).

Table 1. Screening of the reaction condition using a model reaction [(a)].



Entry	Catalyst (mol%)	MnO_2 (equiv.)	Yield (%) [(b)]
1	$HAuCl_4 \cdot 3H_2O$ (5)	5	>99
2	CuI (5)	5	61
3	ZnI_2 (5)	5	46
4	CuCl (5)	5	34
5	CF_3COOAg (5)	5	93
6	$HAuCl_4 \cdot 3H_2O$ (4)	5	>99
7	$HAuCl_4 \cdot 3H_2O$ (3)	5	>99
8	$HAuCl_4 \cdot 3H_2O$ (2)	5	>99
9	$HAuCl_4 \cdot 3H_2O$ (1)	5	>99
10	$HAuCl_4 \cdot 3H_2O$ (3)	4	>99
11	$HAuCl_4 \cdot 3H_2O$ (2)	3	>99
12	$HAuCl_4 \cdot 3H_2O$ (2)	2	75
13	$HAuCl_4 \cdot 3H_2O$ (2)	1	44

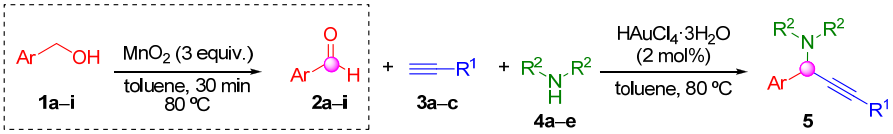
[(a)] Otherwise indicated: benzyl alcohol **1a** (0.5 mmol) was solved in 0.5 mL of toluene and MnO_2 (1–5 equiv.) was further added. Then, the oxidation step was performed at 80 °C for 30 min. Subsequently, $HAuCl_4 \cdot 3H_2O$ (1–5 mol%), piperidine **4a** (0.55 mmol) and phenylacetylene **3a** (0.6 mmol) were added to the same vessel at 80 °C for 2.5 h. [(b)] Yields calculated by ^{1}H-NMR vs the aldehyde as the limiting reagent.

In a second step, we studied the variation of catalyst loading, using $HAuCl_4 \cdot 3H_2O$ from 5 to 1 mol% (Table 1, entries 1, 6–9). In all cases, the final products were obtained with excellent results after a short reaction time (3 h). At this point, we decided to continue with 2 mol% of gold in the subsequent study. Finally, we explored in more detail the oxidation of benzylic alcohol **1a** to give the corresponding benzaldehyde **2a** with different amounts of

MnO_2 (Table 1, entries 10–13). To our delight, the best conditions were obtained using only 3 equiv. of MnO_2 in toluene at 80 °C and after only 30 min of reaction for the oxidation step. It is worth noting that the normal conditions using MnO_2 in other oxidation processes of benzyl alcohols required longer reaction times (1 to 70 h or longer) and greater amounts of equivalents of MnO_2 (between 5 and 20) [12]. Therefore, we have successfully achieved to smooth the reaction conditions for this step, considerably decreasing the necessary amount of oxidation source.

With the best reaction conditions in hand, we explored the viability of our working hypothesis studying the scope of the reaction using different alcohols **1**, alkynes **3** and amines **4** (Table 2).

Table 2. Scope of the one-pot/multicomponent preparation of propargylamines **5** [(a)].



Entry	Ar (1)	R^1 (3)	Amine (4)	Time (h)	Yield (%) [(b)]
1	Ph, **1a**	Ph, **3a**	Piperidine, **4a**	3	97
2	4-MeC_6H_4, **1b**	Ph, **3a**	Piperidine, **4a**	6	87
3 [(c)]	1-naphthyl, **1c**	Ph, **3a**	Piperidine, **4a**	4	90
4 [(d)]	3-$NO_2C_6H_4$, **1d**	Ph, **3a**	Piperidine, **4a**	3	90
5	4-BrC_6H_4, **1e**	Ph, **3a**	Piperidine, **4a**	6	94
6	4-ClC_6H_4, **1f**	Ph, **3a**	Piperidine, **4a**	3	93
7	3-ClC_6H_4, **1g**	Ph, **3a**	Piperidine, **4a**	3	98
8	4-FC_6H_4, **1h**	Ph, **3a**	Piperidine, **4a**	3	94
9	Ph, **1a**	Ph, **3a**	Pyrrolidine, **4b**	4	98
10	Ph, **1a**	Ph, **3a**	Morpholine, **4c**	3	96
11	4-CNC_6H_4, **1i**	Ph, **3a**	Morpholine, **4c**	6	85
12	Ph, **1a**	Ph, **3a**	Bu_2NH, **4d**	18	95
13	Ph, **1a**	Ph, **3a**	Et_2NH, **4e**	18	96
14 [(c)]	Ph, **1a**	4-MeC_6H_4, **3b**	Piperidine, **4a**	5	98
15 [(c,e)]	Ph, **1a**	Me_3Si, **3c**	Piperidine, **4a**	18	98
16 [(f)]	Ph, **1a**	Ph, **3a**	Piperidine, **4a**	6	95

[(a)] Alcohol **1a–i** (0.5 mmol) was solved in 0.5 mL of toluene and MnO_2 (1.5 mmol, 144.9 mg) was further added. Then, the oxidation step was performed at 80 °C for 30 min. Subsequently, $HAuCl_4 \cdot 3H_2O$ (2 mol%), amine **4a–e** (0.55 mmol) and alkyne **3a–c** (0.6 mmol) were added to the same vessel at 80 °C for the necessary reaction time. [(b)] Isolated yield after column chromatography (neutral alumina, *n*-hexane:diethylether 95:5). [(c)] Using 3 mol% of $HAuCl_4 \cdot 3H_2O$. [(d)] The oxidation step takes 1 h to be completed. [(e)] Using 2 equiv. of ethynyltrimethylsilane **3c**. [(f)] For a preparative scale, 4 mmol of **1a** is used.

In general, the final propargylamines **5** were obtained with very good yields (up to 98%) after column chromatography. The results do not suggest a clear correlation between the reactivity of the process with the electronic properties of the starting alcohols. However, it can be inferred that there is a slightly reduced reactivity when the *in situ*-generated aldehydes bear electron donor substituents, as would be expected (see **1b** and **1c**, entries 2 and 3). Interestingly, the reaction worked well for different cyclic and non-cyclic secondary amines (**4a–e**) and various alkynes (**3a–c**), obtaining in all cases almost quantitative yields (>95%). It is remarkable that this catalytic system allows for scaling up the reaction, since the same excellent result, in terms of reactivity, was obtained when the reaction was scaled up 8 times (Table 2, entry 16).

The structures of the final products of this protocol have been also confirmed by the single-crystal analysis of compounds **5aaa** and **5caa** (Figure 2).

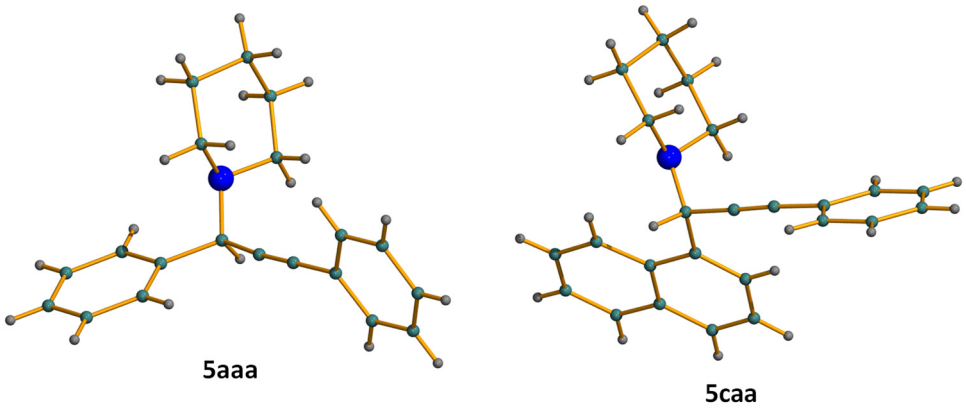
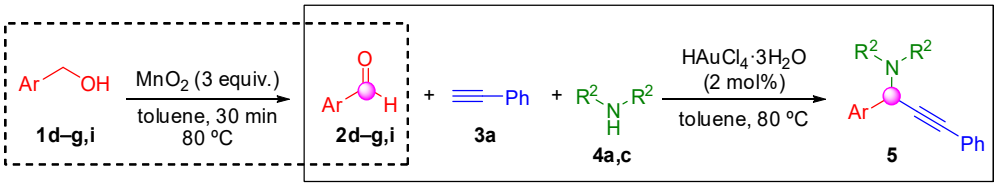


Figure 2. X-ray crystal structures of **5aaa** and **5caa**.

In order to prove that our methodology is efficient and that it could be the best option, we have compared the results of the process starting from the alcohol **1d–g,i** or from the corresponding commercially available aldehyde (without purification) **2d–g,i** (Table 3).

Table 3. Comparative one-pot/multicomponent process starting from the alcohol **1d–g,i** and the aldehyde **2d–g,i** [a,b].

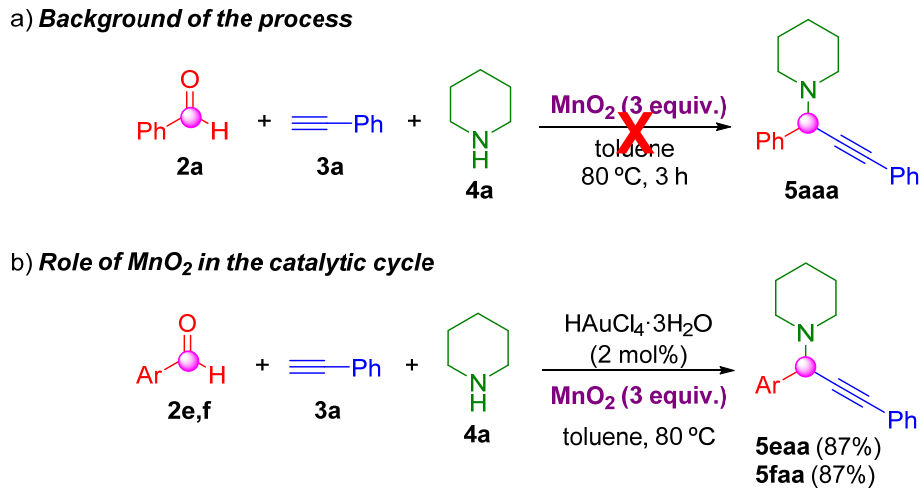


Entry	Ar	Amine (4)	Time (h)	Yield (%) [c]
1	3-$NO_2C_6H_4$, **1d**	Piperidine, **4a**	3	94
2	3-$NO_2C_6H_4$, **2d**	Piperidine, **4a**	3	81
3	4-BrC_6H_4, **1e**	Piperidine, **4a**	6	96
4	4-BrC_6H_4, **2e**	Piperidine, **4a**	6	85
5	4-ClC_6H_4, **1f**	Piperidine, **4a**	3	96
6	4-ClC_6H_4, **2f**	Piperidine, **4a**	3	88
7	3-ClC_6H_4, **1g**	Piperidine, **4a**	3	>99
8	3-ClC_6H_4, **2g**	Piperidine, **4a**	3	86
9	4-CNC_6H_4, **1i**	Morpholine, **4c**	6	90
10	4-CNC_6H_4, **2i**	Morpholine, **4c**	6	45

[a] Alcohol **1d–g,i** (0.5 mmol) was solved in 0.5 mL of toluene and MnO_2 (1.5 mmol, 144.9 mg) was further added. Then, the oxidation step was performed at 80 °C for 30 min. Subsequently, $HAuCl_4{\cdot}3H_2O$ (2 mol%), amine **4a,c** (0.55 mmol) and alkyne **3a** (0.6 mmol) were added to the same vessel at 80 °C for the necessary reaction time. [b] $HAuCl_4{\cdot}3H_2O$ (2 mol%) was solved in 0.5 mL of toluene and then, aldehyde **2d–g,i** (0.5 mmol), amine **4a,c** (0.55 mmol) and alkyne **3a** (0.6 mmol) were added at 80 °C for the necessary reaction time. [c] Conversion by ^{1}H-NMR with respect to the aldehyde.

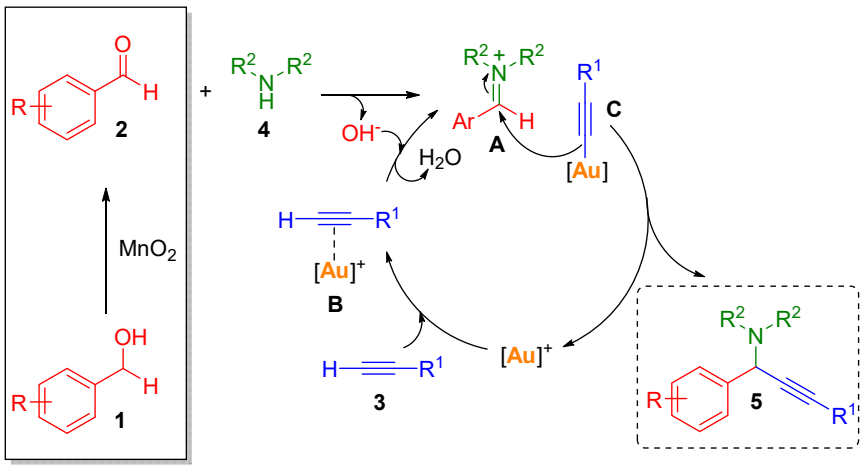
It is remarkable that starting from the alcohols **1d–g,i**, the reaction gives rise to better conversions in all cases after the same reaction time, in comparison with aldehydes **2d–g,i**. Hence, quantitative conversions are obtained with alcohols, while the reactions with the aldehydes are slower. As commented in the Introduction Section, it is well-known that aldehydes have traces of acid, generated in the bottle of the reagents over time. However, we believe that these traces are not generated during the oxidation step, since between the in situ generation of the aldehyde and the successive catalytic gold process, where the aldehyde is consumed, only a short time goes by (3–18 h). Therefore, when aldehydes are used, these traces can influence the reactivity of the process and, consequently, the yield of the reaction, supporting the differences found, as we previously observed for other different processes [13,14].

Additionally, in order to know if the MnO_2 can participate somehow in the successive catalytic step, beyond the oxidation step, we have first performed a background reaction starting from aldehyde **2a** and in the absence of gold (Scheme 2a). However, the propargylamine is not formed. Therefore, the MnO_2 does not catalyze the process by itself alone and the gold catalyst is necessary. An additional proof has been carried out, also adding 3 equiv. of MnO_2 in the catalytic gold reaction starting from aldehyde **2e** and **2f** (Scheme 2b) in order to know if the presence of MnO_2 in the medium can increase the yield of the reaction. In these cases, almost the same conversions were found (87% and 87%) as those reported in entries 4 and 6 (Table 3), respectively. Therefore, we can discard, as far as we know, the role and participation of the MnO_2 in the successive steps of the catalytic mechanism, neither catalyzing the formation of the propargylamine by itself nor helping in some of the steps of the catalytic cycle. These findings support the use of alcohols in many processes instead of the corresponding aldehydes, as a more convenient, stable and easier to handle reagent, and the importance of our developed methodology.



Scheme 2. Role of MnO_2 in the synthesis of propargylamines starting from aldehydes.

Furthermore, on the bases of the experimental results and in previous works [54,55], a plausible reaction mechanism is depicted in Scheme 3.



Scheme 3. Plausible reaction pathways.

After an *in situ* oxidation of the alcohol, the generated aldehyde **2** initially reacts with the secondary amine, giving rise to the iminium ion **A**. A concomitant step is the formation of a π-metal–alkyne intermediate **B**, involving a C–H activation of the alkyne by the gold catalyst. Complex **B** should make the alkyne proton more acidic for further

abstraction. The *in situ*-generated metal acetylide **C** reacts with the iminium ion **A**, leading to the formation of the propargylamines **5**, releasing the gold catalyst for the subsequent catalytic cycle (Scheme 3).

3. Materials and Methods

Purification of reaction products was carried out by column chromatography using silica-gel (0.063–0.200 mm). Analytical thin-layer chromatography was performed on 0.25 mm silica gel 60-F plates. ESI (electrospray ionization) and MicroTof-Q mass analyzer (Zaragoza, Spain) were used for HRMS (high resolution mass spectrometry) measurements. ^{1}H NMR spectra were recorded at room temperature on a BRUKER AVANCE 400 spectrometer (Zaragoza, Spain) (^{1}H, 400 MHz) or on a BRUKER AVANCE II 300 spectrometer (Zaragoza, Spain) (^{1}H, 300 MHz), with chemical shifts (ppm) reported relative to the solvent peaks of the deuterated solvent. $CDCl_3$, CD_3CN and CD_3COCD_3 were used as the deuterated solvents. Chemical shifts were reported in the δ scale relative to residual $CHCl_3$ (7.28 ppm), CH_3CN (1.94 ppm) and CH_3COCH_3 (2.05 ppm) for ^{1}H-NMR and to the central line of $CDCl_3$ (77.16 ppm), CD_3CN (1.32 ppm) and CD_3COCD_3 (29.84 ppm) for ^{13}C-APT NMR.

All reactions were performed under air atmosphere and solvents and reagents were used as received without further purification or drying. All reagents were commercially available.

The spectroscopic data recorded for the products obtained: **5aaa** [72], **5baa** [73], **5caa** [74], **5daa** [75], **5eaa** [74], **5faa** [74], **5gaa** [73], **5haa** [75], **5aab** [76], **5aac** [75], **5iac** [77], **5aad** [78], **5aae** [79], **5aba** [77] and **5aca** [77], are in agreement with values previously reported by other authors. However, we report in the Supplementary Material the ^{1}H NMR and ^{13}C-APT NMR spectra for each final compound as a proof of their obtainment.

3.1. General Procedure for the Au-Catalyzed One-Pot/Multicomponent A^3 Synthesis of Propargylamines **5**

Alcohol **1a–i** (0.5 mmol) was solved in 0.5 mL of toluene and MnO_2 (1.5 mmol, 144.9 mg) was further added. Then, the oxidation step was performed at 80 °C for 30 min. Subsequently, $HAuCl_4 \cdot 3H_2O$ (2 mol%), amine **4a–e** (0.55 mmol) and alkyne **3a–c** (0.6 mmol) were added to the same vessel at 80 °C for the necessary reaction time (Table 2). When the reaction is over, the remaining MnO_2 is filtered, washing the crude with AcOEt, the solvent was evaporated under vacuum, and the extract was purified by column chromatography (neutral alumina, *n*-hexane:diethylether 95:5), giving rise to the corresponding final adducts **5** with very good results.

3.2. Characterization of Propargylamines **5**

1-(1,3-Diphenylprop-2-ynyl)piperidine (**5aaa**) [72]: Following the general procedure described in Table 2, compound **5aaa** was isolated by column chromatography after 3 h of reaction at 80 °C as a yellow solid in 97% yield. HRMS (ESI+) calcd for $C_{20}H_{21}N$ 276.1747; found 276.1739 [M + H].

1-(3-Phenyl-1-*p*-tolylprop-2-ynyl)piperidine (**5baa**) [73]: Following the general procedure described in Table 2, compound **5baa** was isolated by column chromatography after 6 h of reaction at 80 °C as a yellow solid in 87% yield. HRMS (ESI+) calcd for $C_{21}H_{24}N$ 290.1903; found 290.1910 [M + H].

1-(1-(Naphthalen-1-yl)-3-phenylprop-2-ynyl)piperidine (**5caa**) [74]: Following the general procedure described in Table 2 but using 3 mol% of $HAuCl_4 \cdot 3H_2O$, compound **5caa** was isolated by column chromatography after 4 h of reaction at 80 °C as a yellow solid in 90% yield. HRMS (ESI+) calcd for $C_{24}H_{24}N$ 326.1903; found 326.1891 [M + H].

1-(1-(3-Nitrophenyl)-3-phenylprop-2-ynyl)piperidine (**5daa**) [75]: Following the general procedure described in Table 2, compound **5daa** was isolated by column chromatography after 3 h of reaction at 80 °C as a yellow solid in 90% yield. HRMS (ESI+) calcd for $C_{20}H_{21}N_2O_2$ 321.1598; found 321.1586 [M + H].

1-(1-(4-Bromophenyl)-3-phenylprop-2-ynyl)piperidine (**5eaa**) [74]: Following the general procedure described in Table 2, compound **5eaa** was isolated by column chromatography after 6 h of reaction at 80 °C as a yellow solid in 94% yield. HRMS (ESI+) calcd for $C_{20}H_{21}BrN$ 354.0852; found 354.0851 [M + H].

1-(1-(4-Chlorophenyl)-3-phenylprop-2-ynyl)piperidine (**5faa**) [74]: Following the general procedure described in Table 2, compound **5faa** was isolated by column chromatography after 3 h of reaction at 80 °C as a yellow solid in 93% yield. HRMS (ESI+) calcd for $C_{20}H_{21}ClN$ 310.1357; found 310.1346 [M + H].

1-(1-(3-Chlorophenyl)-3-phenylprop-2-ynyl)piperidine (**5gaa**) [73]: Following the general procedure described in Table 2, compound **5gaa** was isolated by column chromatography after 3 h of reaction at 80 °C as a yellow solid in 98% yield. HRMS (ESI+) calcd for $C_{20}H_{21}ClN$ 310.1357; found 310.1357 [M + H].

1-(1-(4-Fluorophenyl)-3-phenylprop-2-ynyl)piperidine (**5haa**) [75]: Following the general procedure described in Table 2, compound **5haa** was isolated by column chromatography after 3 h of reaction at 80 °C as a yellow solid in 94% yield. HRMS (ESI+) calcd for $C_{20}H_{21}FN$ 294.1653; found 294.1641 [M + H].

1-(1,3-Diphenylprop-2-ynyl)pyrrolidine (**5aab**) [76]: Following the general procedure described in Table 2, compound **5aab** was isolated by column chromatography after 4 h of reaction at 80 °C as a yellow solid in 98% yield. HRMS (ESI+) calcd for $C_{19}H_{20}N$ 262.1590; found 262.1594 [M + H].

4-(1,3-Diphenylprop-2-ynyl)morpholine (**5aac**) [75]: Following the general procedure described in Table 2, compound **5aac** was isolated by column chromatography after 3 h of reaction at 80 °C as a yellow solid in 96% yield. HRMS (ESI+) calcd for $C_{19}H_{20}NO$ 278.1539; found 278.1528 [M + H].

4-(1,3-diphenylprop-2-yn-1-yl)morpholine (**5iac**) [77]: Following the general procedure described in Table 2, compound **5iac** was isolated by column chromatography after 6 h of reaction at 80 °C as a yellow solid in 85% yield. HRMS (ESI+) calcd for $C_{20}H_{19}N_2O$ 303.1492; found 303.1489 [M + H].

N-Butyl-*N*-(1,3-diphenylprop-2-ynyl)butan-1-amine (**5aad**) [78]: Following the general procedure described in Table 2, compound **5aad** was isolated by column chromatography after 18 h of reaction at 80 °C as a yellow solid in 95% yield. HRMS (ESI+) calcd for $C_{23}H_{30}N$ 320.2373; found 320.2362 [M + H].

N,*N*-diethyl-1,3-diphenylprop-2-yn-1-amine (**5aae**) [79]: Following the general procedure described in Table 2, compound **5aae** was isolated by column chromatography after 18 h of reaction at 80 °C as a yellow solid in 96% yield. HRMS (ESI+) calcd for $C_{19}H_{22}N$ 264.1747; found 264.1737 [M + H].

1-(1-Phenyl-3-*p*-tolylprop-2-ynyl)piperidine (**5aba**) [77]: Following the general procedure described in Table 2, compound **5aba** was isolated by column chromatography after 5 h of reaction at 80 °C as a yellow solid in 98% yield. HRMS (ESI+) calcd for $C_{21}H_{24}N$ 290.1903; found 290.1894 [M + H].

1-(1-phenyl-3-(trimethylsilyl)prop-2-ynyl)piperidine (**5aca**) [77]: Following the general procedure described in Table 2, compound **5aca** was isolated by column chromatography after 18 h of reaction at 80 °C as a yellow solid in 98% yield. HRMS (ESI+) calcd for $C_{17}H_{26}NSi$ 272.1829; found 272.1821 [M + H].

3.3. Crystal Structure Determinations

Crystals were mounted in inert oil on glass fibers and transferred to the cold gas stream of a Bruker Apex Duo diffractometer (Zaragoza, Spain), equipped with a low-temperature attachment. Data were collected using monochromated MoKα radiation (λ = 0.71073 Å). Scan type ω. Absorption correction based on multiple scans was applied using SADABS. The structures were solved by direct methods and refined on F^2 using the program SHELXL-2016 [80]. All non-hydrogen atoms were refined anisotropically. CCDC (Cambridge Crystallographic Data Centre) deposition numbers 2067799 (**5aaa**) and 2067800

(**5caa**) contain the supplementary crystallographic data. These data can be obtained free of charge by The Cambridge Crystallography Data Center.

4. Conclusions

The results reported in this manuscript represent a straightforward and sustainable synthesis of propargylamines, compounds of extraordinary importance in pharmaceutical chemistry, starting from readily available alcohols. The procedure progresses with excellent yields in a short time and using commercially available oxidant and catalyst. We showed that it is not only possible to avoid starting directly from aldehydes for the preparation of propargylamines, but also the atomic economy and yield efficiency properties are preserved maintaining the original characteristics of a one-pot protocol followed by a MCR process. This one-pot/multicomponent reaction starting from alcohols to generate aldehydes and a subsequent cascade reaction with amines and alkynes to reach the desired final products under gold catalysis could be considered as a formal A^3-coupling reaction. Our developed procedure represents a pivotal example of this undeveloped approach.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/catal11040513/s1, Figure S1: ^{1}H and ^{13}C-APT (CD_3COCD_3) NMR spectra of 1-(1,3-diphenylprop-2-ynyl)piperidine (**5aaa**), Figure S2: ^{1}H ($CDCl_3$) and ^{13}C-APT (CD_3CN) NMR spectra of 1-(3-phenyl-1-*p*-tolylprop-2-ynyl)piperidine (**5baa**), Figure S3: ^{1}H (CD_3COCD_3) and ^{13}C-APT (CD_3CN) NMR spectra of 1-(1-(naphthalen-1-yl)-3-phenylprop-2-ynyl)piperidine (**5caa**), Figure S4: ^{1}H and ^{13}C-APT (CD_3CN) NMR spectra of 1-(1-(3-nitrophenyl)-3-phenylprop-2-ynyl)piperidine (**5daa**), Figure S5: ^{1}H and ^{13}C-APT (CD_3CN) NMR spectra of 1-(1-(4-bromophenyl)-3-phenylprop-2-ynyl)piperidine (**5eaa**), **Figure S6**: ^{1}H and ^{13}C-APT (CD_3COCD_3) NMR spectra of 1-(1-(4-chlorophenyl)-3-phenylprop-2-ynyl)piperidine (**5faa**), Figure S7: ^{1}H and ^{13}C-APT (CD_3CN) NMR spectra of 1-(1-(3-chlorophenyl)-3-phenylprop-2-ynyl)piperidine (**5gaa**), Figure S8: ^{1}H and ^{13}C-APT (CD_3CN) NMR spectra of 1-(1-(4-fluorophenyl)-3-phenylprop-2-ynyl)piperidine (**5haa**), Figure S9: ^{1}H ($CDCl_3$) and ^{13}C-APT (CD_3CN) NMR spectra of 1-(1,3-diphenylprop-2-ynyl)pyrrolidine (**5aab**), Figure S10: ^{1}H and ^{13}C-APT (CD_3CN) NMR spectra of 4-(1,3-diphenylprop-2-ynyl)morpholine (**5aac**), Figure S11: ^{1}H and ^{13}C-APT (CD_3CN) NMR spectra of 4-(1-morpholino-3-phenylprop-2-yn-1-yl)benzonitrile (**5iac**), Figure S12: ^{1}H ($CDCl_3$) and ^{13}C-APT (CD_3CN) NMR spectra of *N*-butyl-*N*-(1,3-diphenylprop-2-ynyl)butan-1-amine (**5aad**), Figure S13: ^{1}H and ^{13}C-APT (CD_3CN) NMR spectra of *N*,*N*-diethyl-1,3-diphenylprop-2-yn-1-amine (**5aae**), Figure S14: ^{1}H and ^{13}C-APT (CD_3CN) NMR spectra of 1-(1-phenyl-3-*p*-tolylprop-2-ynyl)piperidine (**5aba**), Figure S15: ^{1}H ($CDCl_3$) and ^{13}C-APT (CD_3CN) NMR spectra of 1-(1-phenyl-3-(trimethylsilyl)prop-2-ynyl)piperidine (**5aca**).

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