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Gold-Nanoparticle-Catalyzed Synthesis of Propargylamines: The Traditional A^3-Multicomponent Reaction Performed as a Two-Step Flow Process

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Abstract: The alkyne, aldehyde, amine A^3-coupling reaction, a traditional multicomponent reaction (MCR), has been investigated as a two-step flow process. The implicated aminoalkylation reaction of phenylacetylene with appropriate aldimine intermediates was catalyzed by gold nanoparticles impregnated on alumina. The aldimine formation was catalyzed by Montmorillonite K10 beforehand. The performance of the process has been investigated with respect to different reaction regimes. Usually, the A^3-multicomponent reaction is performed as a "one-pot" process. Diversity-oriented syntheses using MCRs often have the shortcoming that only low selectivity and low yields are achieved. We have used a flow-chemistry approach to perform the A^3-MCR in a sequential manner. In this way, the reaction performance was significantly enhanced in terms of shortened reaction time, and the desired propargylamines were obtained in high yields.

Keywords: flow chemistry · gold · multicomponent reactions · nanoparticles · packed-bed capillary reactor · propargylamines

Introduction

Multicomponent reactions (MCRs), such as the A^3-reaction,[1] enable the formation of complex molecules in just one reaction step. High molecular diversity can thereby be obtained because different building block combinations enable easy variation of the moieties on the final molecule.[2] MCRs[3] such as the Ugi reaction,[4] the Mannich reaction,[5] or the Biginelli reaction,[6] for example, offer great potential for diversity-oriented synthesis. However, the mechanisms of MCRs involve different intermediate states that have to be traversed sequentially en route to the final product. The consequent complexity of the reaction sometimes results in low yields and low selectivity in favor of the desired product, thus necessitating the application of costly separation procedures. The intensification of MCRs by heating to improve the kinetics is difficult because the reaction selectivity of the involved intermediate states may get lost. Carrying out the desired reaction steps by the sequential addition of the building blocks to the reaction flask can help to overcome this problem. In such "one-pot" reactions, a necessary catalyst for one reaction step cannot be kept apart from subsequent reaction steps that may be disturbed by this catalyst. Hence, catalyzed one-pot strategies will only be successful if the applied catalysts are compatible with all intermediate reaction steps. The immobilization of catalysts on solid supports enables heterogeneous catalyzed reactions to be conducted even in flow processes.[7] A great variety of catalysts and support materials is available. Flow chemistry uses micro reaction technologies to carry out chemical reactions under controlled-flow conditions.[8] The sequential application of different heterogeneous catalysts in a continuous-flow system allows MCRs to be conducted in a stepwise manner without a change of solvent. In this way, different catalysts can be applied for the individual reaction steps without detrimental influence on previous or subsequent reaction steps. Solutions of building blocks can be introduced into the flow system just before the catalyst. Side reactions by interference of unreacted building blocks with other reaction intermediates can also be circumvented by adopting this approach. The application of a micro flow system enables fast temperature changes so that different temperatures can be applied for each reaction step. Individual optimization of the reaction selectivity and kinetics of each step can improve the efficiency of the overall MCR sequence.[9] Some examples of MCRs in micro flow-through reactors have been described previously.[10] However, the solvent and energy consumptions of sequential MCR processing appear to be comparable to those of the equivalent batch processes. Nevertheless, in terms of green chemistry aspects, the flow-chemistry approach seems to be advantageous because the overall reaction yields may be considerably enhanced.

Propargylamine derivatives (**5**) are interesting molecules for drug screening, useful intermediates for heterocycle synthesis, and are involved in many different synthetic strategies.[11] The three-component coupling reaction of aldehyde (**1**), amine (**2**), and alkyne (**4**) building blocks furnishes

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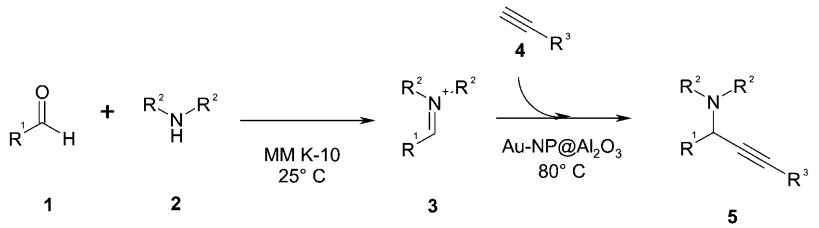
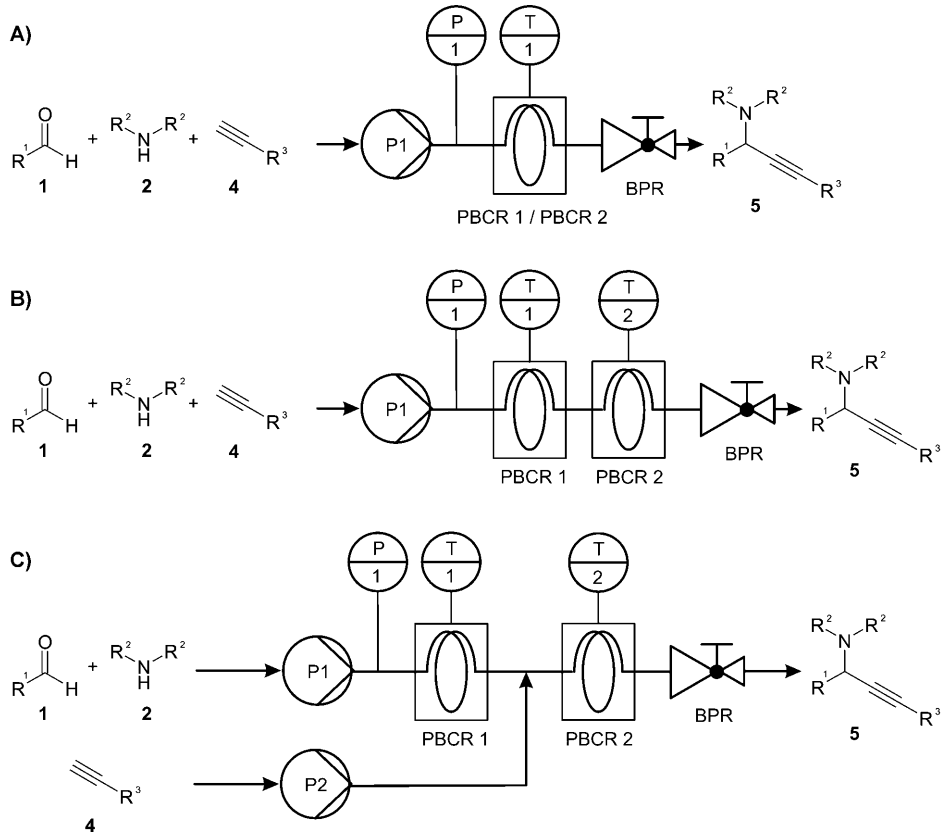


Scheme 1. Aminoalkylation of alkynes (**4**) by the aldimine intermediate **3** in a two-step reaction sequence. Two different heterogeneous catalysts (Montmorillonite K-10, Au-NP@Al_2O_3) were applied sequentially at different reaction temperatures.

propargylamine derivatives of type **5** (Scheme 1). The necessary two-step pathway for this reaction involves addition of the alkyne (**4**) to an aldimine intermediate (**3**). Hence, the initial reaction step involves the formation of the aldimine (**3**) intermediate by condensation of an aldehyde (**1**) and an amine (**2**) prior to addition of the alkyne (**4**). The initial condensation can be promoted by Lewis or Brønsted acids, whereas the second reaction step needs transition metal catalysis. Several catalysts have been employed to assist the A^3-reaction by C–H activation. Various metal ions, such as Fe^{III},[12] Cu^{I},[13] Ag^{I}, and Au^{I}/Au^{III},[14] as well as Ir, In, and Zn[15] compounds, have been investigated as effective catalysts. Various nanoparticular metals[16] and metal oxides[17] have also been investigated as catalysts for the A^3-reaction. Colloidal nanoparticles of Ni, Cu, Ag, and Au were investigated by Kindwai et al.[16,18] Au nanoparticles were found to be highly active. Zhou et al. made use of silver oxide nanoparticles supported on different materials, such as multiwalled nanotubes, diatomite, silica, and alumina.[17b] Superior catalytic performance was observed for the alumina support, but the authors noted a decrease in reactivity after repeated use. Chng et al. made use of Au nanoparticles supported on quantum dots.[19] However, most of the described catalysts need several hours to yield high conversion.[18a,19] To the best of our knowledge, alumina-supported Au nanoparticles have not hitherto been investigated as a catalyst for the A^3-reaction.

Results and Discussion

We have used two different materials to catalyze each reaction step individually. For the initial condensation reaction, Montmorillonite K-10 (MM K-10) was used to produce the aldimine (**3**) precursor. MM K-10 is a clay-based catalyst with combined Brønsted and Lewis acidic activity, and has been used previously as a catalyst for various reactions.[20] For the subsequent alkyne addition step, Au nanoparticles supported on Al_2O_3 (Au-NP@Al_2O_3) were used. To this end, Au nanoparticles of about 2 nm diameter were prepared.[21] Basic alumina powder was then impregnated with these nanoparticles according to a literature procedure[22] (see the Supporting Information). The resulting catalysts were used as obtained, without further calcination or redox activation. Both catalyst materials were used as packed-bed capillary reactors (PBCR) assembled in a bench-top micro flow system (Scheme 2). PBCR1 was filled with MM K-10, and PBCR2 was filled with Au-NP@Al_2O_3. This combination of catalysts has previously been used to good effect for the synthesis of pyridine and polypyridine derivatives.[22,23]



Scheme 2. Flow chemistry set-up schemes for the different reaction regimes A–C. P1, P2 pumps; P(1) pressure sensor; T(1), T(2) temperature sensors; PBCR1 (Montmorillonite K-10) and PBCR2 (Au-NP@Al_2O_3): packed-bed capillary reactors; BPR: back-pressure regulator.

To investigate the performance of the process, the reaction sequence was carried out under different regimes: A) the catalytic potentials of PBCR1 and PBCR2 for the three-component reaction were investigated independently of one another; B) solutions of all three building blocks were mixed and fed sequentially through PBCR1 and PBCR2 at different temperatures; C) the aldehyde and amine building block solutions were mixed and fed through PBCR1, and then the alkyne solution was added to the intermediate product stream before implementation of PBCR2. These set-up modes are illustrated in Scheme 2. In the case of regime C, each solution was fed at the same flow rate. However, the flow rate for PBCR2 was twice that for PBCR1. In other words, the residence time in PBCR2 was half of that in PBCR1.

The product profiles generated under the different reaction regimes were analyzed by LC-MS and studied for particular combinations of building blocks. The regime giving the best reaction performance was optimized in greater detail. Therefore, different reaction temperatures, residence times (flow rates), stoichiometries, and solvents were investigated. The optimized conditions were applied to produce about 25 representative propargylamines using different building blocks.

The conditions for the different reaction regimes were optimized using benzaldehyde (**1a**), piperidine (**2a**), and phenylacetylene (**4**). For reaction regimes A–C, 0.5 mol L^{-1} ethanolic solutions of these compounds were applied at 50 μL min^{-1}. The obtained results are summarized in Table 1. The thermal reaction under regime A without any catalytic support was attempted at up to 150 °C (Table 1, entries 1 and 2), but the desired propargylamine (**5a**) was not observed. The use of Montmorillonite K-10 alone under regime A did not yield the desired product either (Table 1, entries 3 and 4). The use of Au-NP@Al_2O_3 alone (at a loading of 1.25 wt. % Au) yielded the desired product in very small amounts at about 120 °C (Table 1, entries 5 and 6). Hence, the catalytic capabilities of both catalysts were low or absent when they were used independently. Reaction regime B involved subjecting the premixed building blocks to both catalysts sequentially, which enabled the formation of intermediate **3** under MM K-10 catalysis in the presence of phenylacetylene (**4**). When the intermediate reaction mixture passed the second PBCR2, formation of the desired propargylamine (**5**) under Au-NP@Al_2O_3 catalysis was anticipated. However, the observed process performance was low, with only 13 % conversion to **5** (Table 1, entry 7). When the reaction was investigated under flow regime C, the desired product was obtained in a fair yield of about 40 % (Table 1, entry 8). Hence, regime C clearly gave the best reaction performance.

Table 1. Reaction performance in dependence on the reaction regime as shown in Scheme 2 at constant flow rate (0.5 mol L^{-1}, ethanolic solution, 50 μL min^{-1} per feed[a], 1.25 wt. % Au-NP@Al_2O_3).

Entry	Reaction regime	Catalyst	Temp. [°C]	Conv. [%][b]
1	A	no catalyst	80	0
2			150	0
3	A	MM K-10	25	0
4			80	0
5	A	1.25 % Au-NP@Al_2O_3	25	0
6			80	5
7	B	MM K-10 1.25 % Au-NP@Al_2O_3	25 80	13
8	C	MM K-10 1.25 % Au-NP@Al_2O_3	25 80	44
9	C	MM K-10 2.5 % Au-NP@Al_2O_3	25 80	97

[a] Fluidic residence times: PBCR1 60 min; PBCR2 30 min. [b] Calculated for benzaldehyde.

We further optimized the reaction regime C by tuning the reaction conditions for both PBCRs separately. First, the initial condensation reaction was investigated. To this end, a premixed ethanolic solution of benzaldehyde (**1a**) and piperidine (**2a**) was fed through the first PBCR1 and the intermediate reaction product **3** was analyzed by GC-MS. Reactant concentrations of 0.5 mol L^{-1} were used. The reaction profile of the intermediate aldimine (**3**) was analyzed with respect to the flow rate and the temperature. It was found that near-quantitative conversion was achieved at ambient temperature (about 25 °C) and 60 min residence time (50 μL min^{-1}) (Figure 1a). Elevated temperatures (40–100 °C) led to significantly decreased yields. Hence, PBCR1 was used at ambient temperature.

The second reaction step catalyzed by Au-NP@Al_2O_3 was investigated with respect to the reaction temperature, flow rate, and catalyst loading. Motivated by literature reports, we carried out the reaction with 1.5 equivalents of phenylacetylene (**4**) at 80 °C. The obtained conversions are shown in Figure 1b. It was found that complete conversion could not be achieved within 30 min residence time (PBCR2) at a catalyst loading of about 1.25 wt. % Au. However, a loading of about 2.5 wt. % Au led to full conversion of the aldehyde (**1a**) within 30 min (Table 1, entry 9). Variation of the reaction temperature led to lower performance at both loading levels (Figure 2). That is to say, the best yield of the desired propargylamine (**5**) was obtained at 80 °C. Finally, we sought to ascertain whether a 1.5-fold stoichiometric excess of phenylacetylene (**4**), as mentioned in many literature reports, was in fact necessary. Reduction of the 1.5 equivalent excess to a stoichiometric ratio proved to have no influence; conversions of about 97 % were observed in both cases. Different solvents (methanol, acetonitrile, toluene, water) were also tested for the overall process, but ethanol was found to be the most effective. In previous studies, the lifetime performance of the Au-NP@Al_2O_3 catalyst was investigated over 48 h. A marginal decrease in the catalytic performance was observed after 12 h of continuous use.[22] Hence, we renewed the catalyst in PBCR2 after 12 h of operation time. To identify any leaching of the Au catalyst, a batch of about 1 mmol of propargylamine (**5a**) was synthesized using freshly prepared catalyst. The crude product was concentrated in

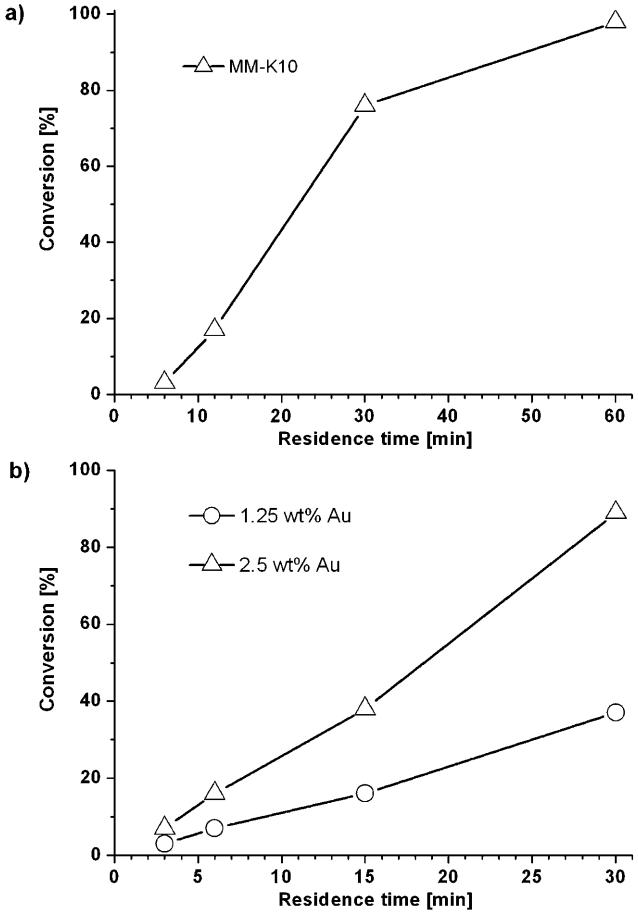


Figure 1. a) Conversion of benzaldehyde (**1a**) to the intermediate aldimine (**3**) determined by GC-MS for PBCR1 (25 °C, flow rates 50–500 μL min^{-1}), b) total product formation determined by HPLC analysis after application of both catalysts according to regime C (PBCR2, 80 °C, flow rates 100–1000 μL min^{-1}).

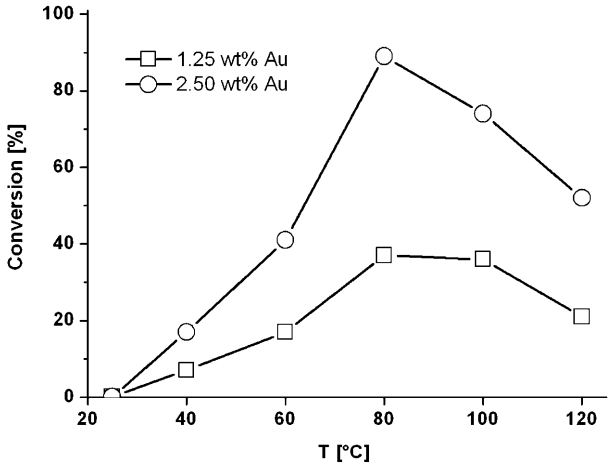
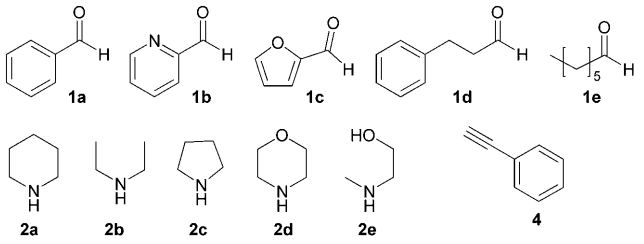


Figure 2. Conversion of benzaldehyde (**1a**) according to regime C determined by HPLC for different reaction temperatures (total flow rate 50 μL min^{-1}).

vacuum at 180 °C overnight and the residue was investigated by EDX analysis. However, no trace of Au was observed.

To demonstrate the potential of the optimized process, different building block combinations were used. The obtained conversions and yields are shown in Table 2. Fair to

Table 2. Results for various building blocks using reaction regime ***C*** (Scheme 1).



Entry	Aldehyde **1**	Amine **2**	Product **5**	Conv. [%][a]	Yield [%][b]
1	**1a**	**2a**	**5a**	97	96
2	**1a**	**2b**	**5b**	54	52
3	**1a**	**2c**	**5c**	95	92
4	**1a**	**2d**	**5d**	91	89
5	**1a**	**2e**	**5e**	88	83
6	**1b**	**2a**	**5f**	99	99
7	**1b**	**2b**	**5g**	85	80
8	**1b**	**2c**	**5h**	97	95
9	**1b**	**2d**	**5i**	88	86
10	**1b**	**2e**	**5j**	92	88
11	**1c**	**2a**	**5k**	70	66
12	**1c**	**2b**	**5l**	43	40
13	**1c**	**2c**	**5m**	53	49
14	**1c**	**2d**	**5n**	70	65
15	**1c**	**2e**	**5o**	56	53
16	**1d**	**2a**	**5p**	99	99
17	**1d**	**2b**	**5q**	99	88
18	**1d**	**2c**	**5r**	93	90
19	**1d**	**2d**	**5s**	99	97
20	**1d**	**2e**	**5t**	99	98
21	**1e**	**2a**	**5u**	92	89
22	**1e**	**2b**	**5v**	80	76
23	**1e**	**2c**	**5w**	99	90
24	**1e**	**2d**	**5x**	99	94
25	**1e**	**2e**	**5y**	99	93

[a] Determined by HPLC. [b] Yield of isolated product after flash chromatography.

excellent yields were obtained. Previously published methods for A^3-coupling have been largely limited to aromatic aldehydes and cyclic aliphatic amines. However, we observed excellent conversions of the investigated aliphatic aldehydes (Table 2, entries 16–25). Cyclic aliphatic amines with five-, six-, and seven-membered rings have been successfully used in previous work. However, acyclic aliphatic amines have only rarely been used for the A^3-reaction and they seem to be difficult building blocks.[10f] We chose two acyclic aliphatic amines: diethylamine (**2b**) and *N*-methyl-2-ethanolamine. In both cases, fair to good yields were obtained. The hydroxyl groups of the obtained propargylamine compounds (**5e**, **5j**, **5o**, **5t**, and **5y**) were found to be unaffected. Excellent yields of the desired propargylamine deriv-

atives (**5**) were obtained even when acyclic amines were used in combination with aliphatic aldehydes (Table 2, entries 17, 20, 22, and 25). The flow regime clearly had a significant influence on the reaction performance. Neither catalyst was able to catalyze the multicomponent reaction independently (Table 1, entries 1–5). Even the serial arrangement of the catalysts under flow regime B showed only a low reaction performance (Table 1, entry 7). Only flow regime C was able to exploit the full potential of both catalysts. Significant reaction intensification in terms of reduced reaction times (60 min for the first step, 30 min for the second step), as well as good conversion of demanding building blocks, was achieved by utilization of the flow-chemistry technique.

Conclusion

MCRs are usually carried out as one-pot reactions. Thereby, detrimental interferences between the different reaction intermediates and the catalysts or other building blocks often lead to low selectivity and poor yields. Serial performance of the respective reaction steps by means of flow chemistry enables processing under reaction regimes that prevent such detrimental interferences between reagents and catalysts. Each reaction step can be optimized separately and finally arranged as a flow-through system without a change of solvent. We have verified this recent concept for the traditional A^3-MCR.

The A^3-coupling reaction was investigated under heterogeneous catalysis in a two-step micro flow-through system. The A^3-reaction mechanism involves two reaction steps that demand different catalytic supports. We used Montmorillonite K-10 (MM K-10) to promote the initial condensation reaction and Au nanoparticles on an alumina support (Au-NP@Al_2O_3) to catalyze the second aminoalkylation step. The reaction regime was found to have a profound influence on the reaction performance. Neither catalyst was able to catalyze the A^3-reaction independently. Even the sequential application of the two catalysts to the premixed reagents led only to low product formation. Only the serial reaction sequence under reaction regime C led to high yields. Whereas the catalytic potential of supported Au nanoparticles has been extensively studied for oxidation reactions, their alkynophilic potential for the base-free aminoalkylation of alkynes has not hitherto been described. The use of aliphatic aldehydes as well as acyclic aliphatic amines in the flow reaction system led to the desired propargylamines (**5**) in good to excellent yields. A stoichiometric excess of phenylacetylene (**4**) was found to be unnecessary. The presented flow-chemistry approach using a combination of MM-K10 and Au-NP@Al_2O_3 as sequential heterogeneous catalysts further extends the capabilities of the A^3-reaction and demonstrates the intensification of an MCR by adopting such a protocol.

Experimental Section

General procedure for the flow-through preparation of propargylamines (5): The respective aldehydes (**1a–e**) (1.0 mmol, 1.0 equiv), amines (**2a–e**) (1.0 mmol, 1.0 equiv), and phenylacetylene (**4**) (1.0 mmol, 1.0 equiv) were each dissolved in aliquots of anhydrous ethanol (2 mL). PBCR1 (L1 = 50 cm, ID = 1.0 mm) was filled with Montmorillonite K-10 powder (Fluka) (400 mg) and 3 Å molecular sieve beads (Alfa Aesar) (40 mg). PBCR2 (L1 = 50 cm, ID = 1.0 mm) was packed with Au-NP@Al_2O_3 catalyst (380 mg). The continuous-flow reaction system was primed with anhydrous ethanol (20 mL) before use. The ethanolic aldehyde and amine solutions were mixed and fed through PBCR1 at 50 $\mu L\,min^{-1}$. The phenylacetylene (**4**) solution was added at 50 $\mu L\,min^{-1}$ to the intermediate product stream immediately before PBCR2. The crude reaction mixture was collected and analyzed by LC-MS. After evaporation of the solvent under vacuum, the product was purified by flash chromatography.

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